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ADENOID CYSTIC CARCINOMA

GENERALIZED METASTASES IN THREE CASES OF BASAL CELL TYPE *

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Some question has existed as to whether the tumors occasionally designated as adenoid cystic basal cell carcinoma are entitled to a special category. For the most part, the confusion has arisen regarding the relationship of this type of neoplasm to the following cutaneous diseases: epithelioma adenoides cysticum of Brooke and Fordyce, cystic rodent ulcer and the typical basal cell carcinoma as described by Krompecher. One must also distinguish adenoid cystic carcinomas from adenocarcinomas.

Certain tumors from both *cutaneous* and *noncutaneous* sites, presumably arising from basal cells or their derivatives, possess unmistakable adenoid cystic features. Since such tumors may be classed as basal cell carcinomas, there is a general tendency to minimize their lethal qualities. The loss of life occasioned by their possible widespread dissemination, or by direct extension into internal parts, is a point that I wish to emphasize and which induces a review of the subject at this time.

For the sake of convenience and clarity, this paper has been divided into three sections: (1) a review of the pertinent literature, (2) the presentation of data gathered from cases at the Memorial Hospital of New York and (3) a description of instances in which widespread metastases arose, a result apparently not anticipated in this type of tumor.

RÉSUMÉ OF THE LITERATURE

Although Krompecher,[1] in 1900, described the adenoid carcinomas of the skin and mucous membranes, it was not until 1903 [2] that his

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* A preliminary report was presented before the New York Pathological Society on Oct. 11, 1928. In an abstract that appeared in the *Archives of Pathology* (**7**:191 [Jan.] 1929) the term roentgen therapy was erroneously substituted for irradiation therapy. The latter is a more general term and includes radium as well as roentgen therapy. The publication of the article has been withheld in order to make the follow-up more complete on case 3 (see detailed case reports of generalized metastases).

1. Krompecher, E.: Der drüsenartige Oberflächenepithelprebs, Beitr. z. path. Anat. u. z. allg. Path. **1**:28, 1900.

2. Krompecher, E.: Der Basalzellenkrebs, Jena, Gustav Fischer, 1903.

notable contributions concerning basal cell cancer were collected into a single monograph. In this work he took up the task of definitely establishing a place for this group of carcinomas. So far as the skin is concerned, his conclusions have stood the test of time and have been generally accepted. There still remain many dissenting opinions as to other sources (mucous membranes, mammary glands, prostate, renal pelvis and salivary glands).

Krompecher recognized types such as solid, adenoid, cystic and keratinizing and combinations of these. He believed that not only the tumor cells but also the stroma might undergo a hyaline or a mucoid degeneration. He went so far as to remark that some basal cell carcinomas might show a similarity to adenocarcinomas, and no doubt it is due to this resemblance that many of the adenoid cystic carcinomas arising from *noncutaneous* sources are labeled with the histologic diagnosis of adenocarcinoma.

In describing twenty-five cases, Krompecher noted that five contained some squamous features. Except in one patient, however, there were no metastases. Of the remaining twenty, adenoid arrangement was disclosed in six, and five were of the cystic type. The cysts seemed to be the result of horny degeneration, sebaceous gland dissolution, caseous softening of basal cell masses, disintegration of the connective tissue which had been enclosed by the epithelial cells or malformed blood vessels and hair follicles.

Of the case reports, there were three that were interesting. The first patient had a primary carcinoma of the buccal mucous membrane with distant metastases. But there was some horny material in the center of the cell nests, and so it may have been a very cellular, anaplastic, squamous carcinoma. The second patient had a primary carcinoma of the nasal mucous membrane. There were local recurrences after each of two operations, and the process then extended to the frontal and sphenoidal sinuses. Exophthalmos became marked, and death resulted from meningitis. Autopsy was not performed, but the lymph nodes were considered free. Sections of the primary tumor showed a carcinoma of the solid basal cell type. The third case was of interest in that it showed at least two primary tumors, one being above the right eye and the other in the middle of the forehead.

With Krompecher's work as a general basis, it is deemed advisable for the remainder of the résumé, and during the analysis of cases, to divide the material into a *cutaneous* and a *noncutaneous* group. It is well realized that a vast and complicated literature has arisen in connection with tumors arising in or near the skin, and all that can be hoped for in an article of this length is to sift out a few of the important points. Moreover, it is clearly understood that, although certain

characteristics may warrant it, such tumors arising from *noncutaneous* portions of the body are not uniformly accepted by many pathologists as basal cell carcinomas.

CUTANEOUS GROUP

In 1885, Balzer and Ménétrier [3] reported a case which they thought was one of adenomas of the sebaceous glands, but which has since been generally accepted as coming within the category of adenoid cystic epithelioma. One year, later, Balzer and Grandhomme [4] presented a somewhat similar case.

In 1887, Jacquet and Darier [5] recorded the case of a man, aged 26, whose chest and arms were the seats of tumors varying in size from the "head of a pin to a pea." The tumors had been present for eighteen years. Darier thought that they were adenomas derived from sweat glands and that the material within the cysts was of a colloid nature. Accordingly, the term hydradénomes eruptifs was employed. Subsequently, at the International Congress of Dermatology and Syphilology in 1889, Quinquad [6] presented a case of the same general type. He sought a new terminology and arrived at that of cellulome epithélial eruptif. At the same meeting, Jacquet [7] discussed Quinquad's case and also mentioned Besnier and Unna as each having reported one case. Jacquet advanced the opinion that the lesions developed from embryonic epithelium of an indifferent nature, which had been misplaced during fetal life and was later excited into active proliferation. To the disease he gave the name epitheliome kystique bénin de la peau.

In addition to those mentioned, a few other case reports were published, so that by 1892 the stage was well set for the excellent articles of Brooke and Fordyce, each of whom worked and wrote independently. Brooke [8] selected the term epithelioma adenoides cysticum and reported his observations on four cases, in two of which microscopic sections were made. Three of the cases occurred in a mother and her two daughters, aged 50, 18 and 14 years.

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3. Balzer, F., and Ménétrier, P.: Etude sur un cas d'adénomes sébacés de la face et du cuir chevelu, Arch. de physiol. norm. et path. **6**:565, 1885.

4. Balzer, F., and Grandhomme: Nouveau cas d'adénomes sébacés de la face, Arch. de physiol. norm. et path. **8**:93, 1886.

5. Jacquet, L., and Darier: Hydradénomes éruptifs, Ann. de dermat. et syph. **8**:317, 1887.

6. Quinquad: Cellulome épithélial éruptif, Ann. de dermat. et syph. **8**:412, 1887.

7. Jacquet, L.: Epitheliome kystique bénin de la peau, Compt. rend. Cong. internat. de dermat. et syph., 1889, p. 416.

8. Brooke, H. G.: Epithelioma Adenoides Cysticum, Brit. J. Dermat. **4**: 269, 1892.

The lesions had appeared between the ages of 10 and 14 years and consisted of tumors projecting slightly above the surrounding skin and ranging in size from 1 mm. to one-half of a small pea. They had soon grown dark and exhibited a shiny, translucent covering of skin. Nearly all contained one or more milia which were plainly visible to the unaided eye. The size of the milium bore no relation to the size of the tumor. The papules seemed to be intradermal and felt firm but not hard. The lesions were scattered thickly about the nose and eyebrows, thinly on other places and none was seen on the lower limbs. Brooke stated that their course was always slow, but that they might take on a sudden acceleration after many years. According to his cases and those of other workers, neither spontaneous involution nor ulceration had ever been observed. The symptoms, if any, were those of a slight pruritus.

Brooke's microscopic observations are worth repeating. The cysts, which were circular or oval, were filled with a colloid material or with concentric layers of horny epithelium. Their size varied so that some could be detected only with the high power of the microscope, while others were prominent with the low magnification. The cysts were formed from degenerating foci of tumor cells. As this process continued, the cells on the periphery grew more and more flattened. In many places there was thus formed a distinct membrana limitans. Some of the cell masses were separated from the connective tissue by a layer of palisade-like cells which stained more darkly than the rest of the growth. Brooke thought that limitation in the growth of the tumor nodule might be due to a peculiar capsule-like structure formed by the connective tissue.

Fordyce's contribution [9] was equally important. He presented two cases, in a mother and her daughter. In addition to the observations which Brooke had made, Fordyce noted a central depression in a few of the growths. Pigment spots and telangiectases were also seen.

In his histologic description, Fordyce mentioned the strong resemblance of the cell masses to adenomas. The individual cells were similar to those seen in the lower layers of normal epidermis. Linear tracts (formed by two or more cells in width) coursed through the derma, intermingled in a most complicated way and connected the large cell masses with one another. Some of these strands resembled coil gland ducts, but no lumen could be made out. The cysts were either empty or else contained keratohyaline material, deeply pigmented detritus or loose degenerating cells. Some cysts were difficult to distinguish from glands, but they lacked the external limiting membrane. Cysts could be found in the connective tissue without apparent con-

9. Fordyce, J. A.: Multiple Benign Cystic Epithelioma of Skin, J. Cutan. & Genito-Urin. Dis. **10**:459, 1892.

nection with any other structures. The beginning of cystic formation was evident in the central portion of some of the tumor masses. There the cells were extremely pale, often imperfectly stained, and at times only the rim of the nucleus could be seen.

In those tumors which had a central depression, Fordyce could trace a direct connection with the lower layers of the epidermis, and the outer cells of the hair follicles were proliferating. The sebaceous glands seemed independent of the process.

One case of lupus erythematosus and another of rodent ulcer were shown in order to emphasize the close histologic picture between these and multiple benign cystic epithelioma, which was Fordyce's appellation for the disease. He concluded that a distinction can properly be made only from the clinical observations together with the natural history of the disease.

From this point many observers were stimulated into reporting cases, and consequently there developed an extensive literature. I think, however, that with the exception of Savatard's article in 1922, the abstracting of such would be superfluous. I therefore refer the reader to the articles themselves. Henceforth, as a rule, only new or important supporting observations will be given.

Heidingsfeld,[10] in a study devoted to the transitional morphology of benign epitheliomas, expressed the belief that the cysts were formed as a result of colloid degeneration of the tumor cells. Sutton [11] wrote that there were two kinds of cysts in multiple basocellular carcinoma. The primary type was due to degeneration of the epithelial cells and the secondary type was derived from the degeneration of connective tissue which had been enclosed by the epithelial tumor cells. Furthermore, he found colloid degeneration of connective tissue outside of such areas. At a later date, Hazen [12] confirmed the finding of a colloid-like material in the majority of the cysts.

Savatard [13] reported fourteen new cases. One patient of great interest was the elder daughter described by Brooke thirty years before. The disease had steadily progressed. By this time there were large lumpy patches, and some of the single lesions were "as large as a cherry." There was a distinct tumor nodule on the calf of the left leg. It will be recalled that Brooke had emphasized the small size of the lesions

10. Heidingsfeld, M. L.: Benign Epithelioma: A Study of Transitional Morphology, J. A. M. A. **59**:256 (July 27) 1912.

11. Sutton, R. L.: The Histogenesis of Multiple Basocellular Carcinoma, J. A. M. A. **62**:977 (March 28) 1914.

12. Hazen, H. H.: Skin Cancer, St. Louis, C. V. Mosby Company, 1916, pp. 61, 102 and 103.

13. Savatard, Louis: Epithelioma Adenoides Cysticum, Brit. J. Dermat. **34**: 381, 1922.

and their absence from the lower limbs. None of the growths had ulcerated or involuted.

The existence of adenoid cystic epithelioma in the negro race was reported by Sutton.[14] His patient had a remarkable family history. The hereditary nature of the disease has been unmistakable in some well authenticated cases, and in others it has been definitely absent. One can find numerous instances supporting either side of this question.

Ulceration of the supposed benign lesions was early observed by Jarisch[15] and confirmed by Little,[16] Savatard,[13] Dore[17] and others. In Dore's case the lesion may have been malignant.

It is probably true that some of the benign tumors had broken down without showing unrestrained growth, yet on the other hand, practically all of the malignant lesions had an associated or a preceding ulceration. As early as 1890, Hallopeau,[18] reporting what he believed was a case of tumors of sweat gland origin, but which later authors have thought was adenoid cystic epithelioma, mentioned that among the innocent lesions was one that appeared malignant. A section was taken and it was examined by Darier, who pronounced it to be a malignant epithelioma. Four years later a similar observation was made by J. C. White,[19] who noted that coexisting with the benign forms were several broken down skin cancers. Some of these appeared to resemble Hutchinson's crateriform epithelioma, while others seemed to be rodent ulcers. White thought that they had probably originated in the benign lesions, and he ventured to predict that many would undergo such changes if a sufficient period of time was allowed to elapse. These observations were later given adequate support by Hazen,[12] Stelwagon[20] and others. Savatard[13] apparently had such a case which recurred after operation, and he quoted Cranston-Low as citing the case of a patient whose lesions had undergone malignant transformation.

Why innocent tumors should change their character and begin an invasion which threatens the patient's life is an unsolved problem.

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14. Sutton, R. L.: A Differential Study of Multiple Benign Cystic Epithelioma and Adenoma Sebaceum in the Negro, J. Cutan. Dis. **29**:480, 1911.

15. Jarisch: Zur Lehre von den Hautgeschwülsten, Arch. f. Dermat. u. Syph. **28**:163, 1894.

16. Little, E. C. G.: A Note on Two Cases of Epithelioma Adenoides Cysticum (Brooke) Tricho-Epithelioma, Brit. J. Dermat. **26**:173, 1914.

17. Dore: Multiple Benign Cystic Epithelioma (One Case), Brit. J. Dermat. **24**:190, 1912.

18. Hallopeau, M.: Hydradenoma complique d'epithelioma vulgaire, Ann. de dermat. et syph. **1**:872, 1890.

19. White, J. C.: Multiple Benign Cystic Epithelioma (One Case), J. Cutan. & Genito-Urin. Dis. **12**:477, 1894.

20. Stelwagon, H. W.: Treatise on Diseases of the Skin, ed 9, Philadelphia, W. B. Saunders Company, 1921, pp. 680 and 908.

White [19] thought that it might be accounted for by changes associated with the age of the patient, or that it might be due to the invasion of normal cutaneous epithelium which reacted against the tumor in an abnormal way. The line between benignancy and malignancy is often very narrow, as was recognized by Sutton,[21] who reported cases in a mother and daughter. Each had many lesions representative of benign cystic epithelioma. In addition, the mother had a rodent ulcer near the eye where there had been no preexisting lesion; in the daughter, one had developed in a benign lesion on her neck. Sections from the rodent ulcer and from three of the benign lesions had the same histologic picture and would ordinarily have been diagnosed as rodent ulcer.

The origin of tumors belonging to the "adenoid cystic group" will be treated briefly. Most authors have agreed that in all probability they arise from the basal cell layer of the rete pegs or from the sheath of a hair follicle (Wolters,[22] Hartzell,[23] Hazen [12] and others). Heidingsfeld [10] believed that the tumor cells were of a distinct basal cell character, but that any macroscopic lesion had proceeded too far for its genesis to be traced by a microscopic study. He found that structures in the immediate neighborhood of the tumor were undergoing proliferation and that he attributed to a "stimulus beyond the recognizable sphere of morphologic change."

That the skin tumors known as adenoid cystic epitheliomas might often be confused or associated with other lesions was supported by Pick [24] (acne rosacea with adenoma sebaceum), Sequiera [25] (lupus erythematosus) and Savatard [13] (moles). Although the characteristics of this malady have become more clearly defined, there still exists an uncertainty in the minds of some observers. Adenoma sebaceum has been definitely separated, leaving rodent ulcer and syringocystadenomas (the latter to a lesser degree) as the principal diseases to consider in the differential diagnosis.

In this connection it is well to recall that Hallopeau [18] reported his case as hydradenomas (syringocystadenomas). In a differential study

21. Sutton, R. L.: Occurrence of Cancerous Changes in Benign New Growths of the Skin, Am. J. M. Sc. **145**:819, 1913.

22. Wolters: Epithelioma Adenoid Cysticum, Arch. f. Dermat. u. Syph. **56**: 89, 1901.

23. Hartzell, M. B.: Benign Cystic Epithelioma and Its Relationship to So-Called Syringo-Cystadenoma, Syringocystoma, and Haemangio-Endothelioma, Brit. M. J. **11**:991, 1904.

24. Pick: Ueber das Epithelioma adenoides cysticum (Brook) und seine Beziehung zum Adenom der Talgdrusen (Adenoepitheliom), Arch. f. Dermat. u. Syph. **58**:201, 1901.

25. Sequiera: Epithelioma Adenoides Cysticum (Report of 4 Cases), Brit. J. Dermat. **26**:89, 1914.

between this disorder and adenoid cystic epithelioma, J. C. White [26] observed that tumors of sweat gland origin were smaller at high altitudes than at sea level, and that at any given height the sweat secretion was less in the tumor area than in the normal adjacent skin. Histologically, the process appeared to be due to the growth and cystic dilatation of the ducts rather than of the sweat glands proper. In a study of similar purpose, Sutton and Dennie [27] found that the administration of pilocarpine would increase the size of the true syringocystadenomas. Schidachi [28] was able to mimic the tumor process of sweat glands by experimentally occluding the ducts. In the proliferation of the cells thus stimulated, he discovered budding processes and distinct cysts. Therefore, it would appear from these and other studies that tumors of sweat gland origin are probably distinct from "adenoid cystic epitheliomas" found arising from the sheath of hair follicles and the lower basal layer of covering epithelium.

TABLE 1.—*Points of Difference as Listed by Adamson*

Rodent Ulcer	*Adenoid Cystic Epithelioma*
Usually in males	Usually in females
Occurs in later life	Appears in childhood
Not hereditary	Distinct familial tendency
Irregular distribution	Symmetrical distribution
Varying size, no limit	Uniform size, limited
Locally malignant	Not locally malignant

Many interesting discussions have taken place concerning the relationship between rodent ulcer and adenoid cystic epithelioma. There are still some authors who class the two together.

In a differential study directed toward the separation of these two diseases, Adamson,[29] as early as 1908, concluded that the cases reported as adenoid cystic epithelioma by Stelwagon and Jarisch were really rodent ulcers. He believed that the one recorded by White was either a true rodent ulcer or a connecting link between the two disorders. Table 1 lists the chief points of difference as given by Adamson.

Six years later, Adamson [30] reemphasized that rodent ulcers, beside their tendency to ulcerate, usually appeared late in life. In a second

26. White, J. C.: Syringocystoma, J. Cutan. Dis. **49**:49, 1907.

27. Sutton, R. L., and Dennie, C. C.: Possible Interrelationship of Acanthoma Adenoides Cysticum (Multiple Benign Cystic Epithelioma) and Syringocystadenoma (Lymphangioma Tuberosum Multiplex), J. A. M. A. **58**:333 (Feb. 3) 1912.

28. Schidachi, Tominatsu: Experimentelle Erzeugung von Hidrocystomen, Arch. f. Dermat. u. Syph. **83**:3, 1907.

29. Adamson, H. G.: Two Cases of Multiple Rodent Ulcer, Lancet **2**:1133, 1908.

30. Adamson, H. G.: On the Nature of Rodent Ulcer, Lancet **21**:810, 1914.

paper written the same year,[31] he mentioned the similarity between multiple rodent ulcer and adenoid cystic epithelioma.

The points of difference listed by Adamson warrant discussion.

Whether the patient is a male or a female has not been found of sufficient importance to stress.

Sequiera [25] stated that the age distinction was not reliable, for rodent ulcers could start early in life (he reported one case in which the age was 11 years) and were usually confused with lupus vulgaris. Likewise, the appearance of adenoid cystic epithelioma at a later age than commonly thought was supported by Dyer [32] and Hartzell.[33] Ormsby,[34] however, wrote that the occurrence of rodent ulcer at a usually later age was of distinct value in the diagnosis.

The familial tendency of adenoid cystic epithelioma is of some importance and has already been mentioned.

Cases of patients with single lesions of the benign disease have been reported by several investigators. Wolter's case [22] was apparently the first recorded. Savatard [13] concluded that the solitary form of the disorder was more frequent than the multiple variety, but that it was usually overlooked. He quoted Cranston-Low's somewhat analogous observations. Various authors have noted multiple forms of rodent ulcer. However, despite the fact that single and multiple lesions occur in either disease, it is probable that symmetry of distribution in the multiple form points toward adenoid cystic epithelioma.

It has been generally conceded that the benign disease has a greater tendency to uniformity in size and to limitation in growth, but even here exceptions have been reported.

The presence of malignant changes and of ulceration in adenoid cystic epithelioma has already been touched on. Sutton [21] believed that one could depend neither on the ulceration of a lesion nor on the histologic picture to separate one type of neoplasm from the other. Little [16] added to the complexities of the subject by reporting two cases of what he believed to be adenoid cystic epithelioma with ulceration of some of the lesions. In a later article,[35] he mentioned Bland-Sutton as having diagnosed the two conditions in mother and daughter when Little thought that despite the ulcerations both had the benign and not the malignant disease. In contrast to Little's belief, Johnston and

31. Adamson, H. G.: Epithelioma Adenoides Cysticum of Brooke, Brit. J. Dermat. **26**:88, 1914.

32. Dyer, I.: Multiple Benign Cystic Epithelioma, Am. J. Dermat. & Genito-Urin. Dis. **1-2**:52, 1897-1898.

33. Hartzell, M. B.: Benign Cystic Epithelioma: Report of Two Cases Presenting Unusual Features, Am. J. M. Sc. **124**:441, 1902.

34. Ormsby, O. S.: Diseases of the Skin, ed. 3, Philadelphia, Lea & Febiger, 1927, p. 666.

35. Little, E. G. C.: Rodent Ulcer, Brit. J. Dermat. **27**:145, 1915.

Paul [36] in the same year reported a case in which on account of the ulcerations the diagnosis of multiple rodent ulcer was made. They were willing to concede, however, that their case might be one of the so-called connecting link types. Miller [37] reported four cases under the title of benign cystic epithelioma, one of which presented ulcerations. This patient died one year later with bronchopneumonia. It is unfortunate that no autopsy was performed.

Little [35] maintained that the chief distinction between rodent ulcer and adenoid cystic epithelioma was that the former was rare except on the face, but he admitted that extrafacial cases of rodent ulcer had been reported.

Stelwagon [20] listed twelve synonyms for benign cystic epithelioma, these being given in French, German and English. He noted its close relationship in structure to rodent ulcer and reiterated the fact that malignant changes might be superimposed. Therefore, he thought that the prognosis was not always certain.

In contrast with the foregoing authors, others have thought it not uncommon for rodent ulcers to undergo cystic degeneration and thus to present a distinct type. In 1901, Dubreuilh and Auche [38] described such a process. They, together with Hazen,[12] believed that the cysts might be formed from the degeneration of the tumor cells resulting in keratohyaline changes. They observed that sometimes the cavities were very large and numerous. Cystic rodent ulcers have been described by other authors. As late as 1927 Ormsby [34] stated that cystic degeneration of basal cell carcinoma might occur.

It can readily be seen that confusion still exists, and that the separation of adenoid cystic epithelioma and cystic rodent ulcer is sometimes a matter of personal opinion. In two papers [39] Hartzell proposed that the various skin tumors which possessed similar histology should be placed in one group until more accurate studies could be made.

Do Basal Cell Carcinomas Metastasize?—Another question of absorbing interest has been whether a true basal cell carcinoma had the power to metastasize. It has generally been thought that they do not. There are some well authenticated cases, however, which lead one to believe that there are possible exceptions to the rule; yet it is reasonable to suppose that some of these may be accounted for by the fact that some predominantly basal cell carcinomas may contain a few squamous

36. Johnston and Paul: Multiple Rodent Ulcer, M. J. Australia **2**:139, 1915.

37. Miller, J. W.: Multiple Benign Cystic Epithelioma, J. Cutan. Dis. **33**: 462, 1915.

38. Dubreuilh, W. and Auche, B.: De l'ulcus rodens, Ann. de dermat. et syph. **2**:705, 1901.

39. Hartzell, M. B.: Benign Cystic Epithelioma and Its Relationship to So-Called Syringo-Cystadenoma, Syringocystoma, and Haemangio-Endothelioma, Brit. J. Dermat. **16**:361, 1904; footnote 23.

elements, as Broders and MacCarty [40] have pointed out. They wrote that basal cell carcinomas could be found on any surface of the body covered by protective epithelium, and that the lesions presented great variations in cell morphology and arrangement. They were either alveolar, glandlike (even resembling thyroid tissue) or in solid masses, and some might also present combinations of these forms. Prickle cells could be rarely but positively demonstrated. A certain number of basal cells could always be demonstrated in squamous cell carcinoma. As a matter of fact, Broders and MacCarty seemed to think that all tumors arising in protective epithelium came from the basal cell layer and the only feature that distinguished them was their cellular differentiation. Stelwagon [20] made notation to the effect that there was a rare possibility of rodent ulcer involving lymph glands, and that its type might be changed into a deep-seated or papillary form of the disease. In an excellent article on cancer of the skin, Morton [41] pointed out that basal cell carcinoma might conceivably give rise to regional metastases.

Beadles [42] reported a case which presented an extensive rodent ulcer of fifteen years' duration, situated on the upper part of the face, and in which there was definite extension to the lymph nodes beneath the lower jaw. The histology was described as being glandular. There were no solid masses or keratinoid areas. Two years before a similarly involved node had been removed from the neck. There was no invasion of the capsule. Death resulted from septic pneumonia. Dubreuilh and Auche [38] observed a patient who had a rodent ulcer situated on the brow, nose and eyelid, which apparently involved the regional lymph glands. Fordyce [43] recorded the case of a man, aged 60, who had a typical rodent ulcer of ten years' standing. It extended from the side of the nose to the inner canthus of the eye. Coincident with this there was a somewhat similar condition behind the ear. The latter lesion was operated on, and there was a recurrence in the scar. Following this, a lymph node in the region of the mastoid process became enlarged, and the microscopic appearance was identical with that of the primary tumor. Fordyce sought to explain this unusual extension of the disease by the fact that the tumor, situated between bone and dense fibrous tissue, had considerable pressure exerted on it which may have forced some of the cells into the lymphatics. Körbl [44] reported two

40. Broders, A. C., and MacCarty, W. C.: Epithelioma, Surg. Gynec. Obst. **27**:141, 1918.

41. Morton, John J.: Cancer of the Skin, Arch. Surg. **12**:655 (March) 1926.

42. Beadles, C. F.: Rodent Ulcer, Tr. Path. Soc. London **45**:176, 1894.

43. Fordyce, J. A.: Cancer of the Skin, J. Cutan. & Genito-Urin. Dis. **20**: 147, 1902.

44. Körbl, H.: Die Röntgenbehandlung der Haut Carcinom speciell des Basalzellenkrebs, sein histologisches Verhalten vor und nach der Bestrahlung, Arch. f. klin. Chir. **97**:752, 1912.

cases of rodent ulcer which apparently metastasized to adjacent lymph glands. One underwent squamous metaplasia in the lymph node, but the other case retained its pure basal cell character.

It is a singular fact that Hazen [45] should report four cases within one year after he had stated in his textbook that basal cell carcinoma never metastasized and that when glands were reported as involved, there had probably been an error in the diagnosis.[12] In view of the data given, however, only one of Hazen's cases can be fully accepted. In this patient there had been a history of seven years' previous treatment which had resulted in successive healings and subsequent recurrences. No changes in histology were noted, however, and the metastastic tumor was an unmixed basal cell carcinoma. Finnerud [46] had two patients who suffered from basal cell carcinoma of long standing. The lesions had been treated with satisfactory primary results but had repeatedly recurred. Finally, both metastasized to the submaxillary space. Each presented the microscopic picture of basal cell carcinoma in the primary and secondary growths. In the tissue from one of the patients there were distinctly cystic areas.

From the foregoing, it would seem that basal cell carcinoma may rarely extend to the regional lymph nodes. It is hard to ascertain whether any of the reported cases were of the adenoid cystic type, but it would appear that at least two (Finnerud's and Beadle's) may have belonged to that group.

After a careful search through the literature, I have been unable to find any case in which definite, unmixed, basal cell carcinomas arising from the skin gave rise to widespread or distant metastases.

NONCUTANEOUS GROUP

Since a mass of conflicting literature has collected on the subject, and in consideration of certain cases analyzed and reported herein, I wish to emphasize the fact that some eminent pathologists believe that basal cell carcinomas (some of which are of the adenoid cystic type) may arise in places other than the skin.

No attempt will be made to cover fully the literature. The third edition of Ewing's "Neoplastic Diseases" [47] will be the chief source for reference.

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45. Hazen, H. H.: Basal Celled Cancers of the Skin, South. M. J. **10**:241, 1917.

46. Finnerud, C. W.: Metastatic Basal Cell Carcinoma from the Skin, J. A. M. A. **82**:775 (March 8) 1924.

47. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

The maxillary sinus and the nasal mucosa may give rise to carcinoma of the basal cell type. The structure may simulate that of the thyroid gland, or a more compact arrangement may resemble that of adenoid cystic carcinoma. As a rule, the growth is slow, recurrence is persistent after incomplete excision and there may be extension to lymph nodes or bone.

Some of the malignant tumors of the salivary glands are of the basal cell type. It is true as Krompecher [2] stated that some neoplasms of the mucous membrane and other structures as well belong within this group, and some of these in turn may be placed into the adenoid cystic subdivision. The structure and clinical course may follow that of tumors of similar appearance but which arise from the skin. Misplaced bits of epithelium may serve as the source for such growths. These may lie in the orbit, lacrimal duct, buccal mucosa and elsewhere. At times they are confused with endothelioma or adenocarcinoma.

In 1901, Buxton [48] reported a case from the Memorial Hospital in which the tumor had originated at the orifice of Steno's duct. After running a slow course for twenty years, it metastasized to the regional lymph nodes. The histology of the primary and secondary growths was that of adenoid cystic basal cell carcinoma.

In 1916, New [49] called attention to what may have been a similar case. He did not express such an opinion, however, and made no mention of metastasis. In 1918, Broders and MacCarty [40] wrote that some tumors of the palate are composed of cysts, glands and squamous epithelium in varying amounts. In 1919, Broders [50] stated that some tumors arising in the nose, pharynx, antrum, parotid gland, mouth and similar places looked like basal cell carcinoma, but that the trained eye will detect a difference. Just what this difference was, he did not clearly state. He also referred to the fact that the lesions would metastasize; but, again, this was a general notation without being supported by definite personal cases or by reference to other authors. He placed stress on the variations in the histologic structure and expressed the belief that basal cells might take on squamous features.

In 1922, Johnson,[51] from the Memorial Hospital, New York, described seven cases of what he termed aberrant adenoid cystic epi-

48. Buxton, B. H.: Benign Epithelial Tumors of the Skin, Pub. Cornell Univ. M. Coll. Stud. Dept. Path., 1901-1902, vols. 1-2, sect. 5.

49. New, G. B.: Adenoma of the Palate, Ann. Otol. Rhin. & Laryng. **25**:687, 1916.

50. Broders, A. C.: Basal-Cell Epithelioma, J. A. M. A. **72**:856 (March 22) 1919.

51. Johnson, F. M.: Aberrant Adenoid Cystic Epithelioma of the Salivary Gland Type, Ann. Surg. **75**:331, 1922.

thelioma of the salvary gland type. Five were from the palate, one arose from the skin of the upper lip and the other originated from the epidermis of the forehead. Their tendency was neither to ulcerate nor to involve lymph nodes. He thought that they were very amenable to irradiation therapy.

SUMMARY

A rather extensive review of the literature has been made. As a general basis for discussion, Krompecher's classic work on basal cell carcinoma is utilized. Following this, a distinction is made between the tumors of *cutaneous* and *noncutaneous* origin. In the former, an attempt is made to develop the idea that the first reports generally tended to deal with a benign process which occurred in the young, and often exhibited a familial tendency. The factor of ulceration is brought in and naturally leads into a discussion of rodent ulcer. Histogenesis and histology have both brought into the review a limited amount of space devoted to tumors arising from sweat glands or from sebaceous structures. The report of malignant changes reported by some authors has been considered and also the question of metastatic basal cell carcinoma has been dealt with. In the noncutaneous group the lack of uniformity of opinion has been stressed, and certain cases have been given space.

In no case in the literature has there been found a true instance of widespread dissemination of an unquestioned basal cell carcinoma.

ANALYSIS OF CASES

The fifty-eight cases used in this study were selected from a group comprising 185 basal cell carcinomas. These were from cutaneous sites, buccal mucosa, tonsil, nose and antrum. Neoplasms resembling basal cell tumors histologically, but derived from such organs as the cervix or the esophagus, were not studied. Since these are highly malignant and are prone to metastasize readily, from a clinical standpoint they do not fit into the ordinary basal cell type. Furthermore, adenoid cystic forms of these tumors seem rare.

In order to follow the general tendency in past studies and on account of the marked difference in mortality, the adenoid cystic basal cell carcinomas were divided in two groups, *cutaneous* and *noncutaneous*.

CUTANEOUS GROUP

Thirty-seven cases occurred in this group. Seven of these had some squamous features, and they will be analyzed separately.

The age at which the lesion first appeared is given in table 2 in decades. This datum was obtainable in twenty-six cases.

The youngest age at which the lesion appeared was 26, and the oldest, 72 years. The average age throughout the series was 48 years. It will be seen that the ages follow closely those in which basal cell carcinomas of the rodent ulcer type are found.

Sixteen of the thirty cases were in females, and fourteen in males. Thus sex played no important rôle. Furthermore, nationality did not seem to have any bearing. In the twenty-six cases in which nativity could be determined, it seemed to be evenly distributed among the types of people who patronized the hospital. Likewise, occupation assumed a negligible part. People engaged in outdoor pursuits were not as numerous as those who worked where their skin would be less exposed to the elements. This was further supported by the fact that women, who naturally live indoors more than men, slightly outnumbered the men.

Only ten cases could be found in which there was even the slightest suggestion as to etiology. The apparent etiologic factors will be listed,

TABLE 2.—*Age Incidence in Twenty-Six Cases of Cutaneous Group*

Decade	*Number of Patients*
3rd	2
4th	3
5th	12
6th	5
7th	3
8th	1

but no conclusions will be drawn: (1) eczematoid lesions treated twenty-two years before with arsenic; (2) a roofer developed a lesion in the postanal skin; (3) pince nez glasses caused irritation of the nose followed by formation of wartlike lesions which broke down; (4) a barber accidentally clipped off the top of an apparently benign wart which finally healed, but five years later a lesion appeared in about the same place; (5) a tumor developed in or near a scar which had resulted from a wound caused by a wooden splinter; (6) a burn in which incomplete epithelization took place; (7) a burn from a spark of fire which healed but in the scar of which a pimple formed; (8) pressure of eye glass frame on a benign mole of long standing; (9) a "pimple" which was squeezed; (10) a mole which was irritated by scratching. The foregoing factors are merely suggestive, and nothing definite can be deduced from them.

In adenoid cystic epithelioma of the skin competent observers have noted the familial nature of some of the cases, the general tendency of the lesions to remain stationary after slowly reaching 0.5 cm. or less in size and the usual lack of ulceration. The cases in the Memorial

Hospital exhibit no hereditary qualities, and the lesions have progressively spread unless controlled by treatment. In the group of thirty cases, ulceration was absent in five, not mentioned in five and present in twenty. In these twenty it was definitely spontaneous in thirteen, questionably so in four and caused by external agents in three. Therefore, one may assume that spontaneous ulceration in our cases was fairly characteristic of the disease.

Pain was present in only four cases, and then it was very mild. It was definitely absent in eighteen. In seven patients there was no reference to pain, and probably none existed. A slight itching sensation was noted in one case. Consequently, one is led to believe that pain is a negligible factor.

In general, the distribution of the lesions corresponded to that seen in the usual types of basal cell carcinoma. Most of them were located on or about the nose; there were many on or near the eyelids, and some were found on the forehead or adjoining temporal regions. Unusual sites were the forearm, back and neck (one case); buttock (one case), and neck, below and behind ear (one case).

When the disease progressed, it was by local extension. Eight of the thirty cases showed this to a rather marked degree. There was one case which invaded the skull, meninges and brain. Another case (not included in this study) has recently come to notice in which there is invasion of the mandible. Whether the neoplastic cells actively grow into living bone, or whether they merely replace devitalized osseous tissue which has been eroded and atrophied through pressure and infection is an unsettled point; it would appear, however, that the former process is the more probable.

The duration of the lesion before the patients came to the Memorial Hospital was ascertained in twenty-seven cases. The shortest interval was four months (one case), and the longest was thirty years (one case). The average was seven and one-half years. Because of failure to eradicate the lesions when they were small and amenable to treatment, large areas of tissue were destroyed with resulting mutilation, and the duration of the treatment was needlessly prolonged.

A follow-up study was made for at least three years in fifteen cases of unmixed adenoid cystic basal carcinoma; some cases were studied for a much longer period.

Previous treatment had been instituted in twelve of the fifteen cases and consisted in employing everything from salves to surgical intervention and irradiation. As nearly as can be judged, both surgical intervention and irradiation were exercised in a desultory manner. At least they proved effective in the Memorial Hospital under undoubtedly much worse conditions than when the patients first presented them-

selves elsewhere. It seems hardly possible to overemphasize the importance of adequate, early treatment.

In the therapeutic regimen at the Memorial Hospital, external irradiation (usually radium) was employed in every case. This was reinforced by interstitial applications in seven cases. In addition, surgical procedures, varying from the evacuation of the orbit to the excision of small areas of infected or tumor tissue, were employed in eleven cases. It is interesting to note that in all cases in which interstitial irradiation was used there was also surgical intervention. These cases were undoubtedly worse than those in which external irradiation alone sufficed. The number of treatments with irradiation varied from one to twelve, and in the series as a whole each patient had an average of four and one-half treatments. It is possible that the number of treatments could be reduced by employing the x-ray or large radium applicators (pack) instead of using radium in small applicators, for in that way it would be possible to treat a much greater area at one time. The underlying normal tissues, however, would receive more proportionate irradiation, and this would often be a contraindication (as in lesions near the eye or overlying bone). The number of surgical procedures varied from one to about three in each of the eleven patients submitted to them.

The duration of the treatment varied from the necessary requirement for application in two cases to five and one-half years in one case. The average duration for all of the cases taken collectively was two years and two months.

An analysis of the final results reveals that only one patient is known to have died. Her condition was obviously hopeless from the start. The lesion was of ten years' duration and had already destroyed a large part of the left parietal, temporal and frontal bones. She developed hernia cerebri, and this was followed by hemiplegia. Of the remaining fourteen patients, two were lost from observation after being free from apparent disease at the end of four months in one case and of nine years in the other. There were twelve patients alive. One had a definite recurrence after it seemed probable that the disease was controlled; this occurred five years after the first treatment. The subsequent lapse of time has been insufficient to estimate the permanent results of the final treatment. For the eleven patients alive and seemingly well, the period of observation at the Memorial Hospital has varied from three to eight and one-half years, and the average is more than five years.

When one considers the extent of the disease and its duration before treatment here, the results are satisfactory so far as the actual preservation of life goes. However, there were numerous recurrences, and in ten of the fifteen cases in which follow-up studies were made, there

were complications varying from loss of bits of tissue to that of an eye. Some of the patients had sequestrums. The complications could be avoided in only the early cases, and these unpleasant factors serve to strengthen the plea for earlier and more effective treatment.

Mixed Squamous and Adenoid Cystic Basal Cell Carcinoma from Cutaneous Sites.—This group comprises seven cases. The squamous elements were marked in some and slight in others, but were definite in all cases. The adenoid cystic portion did not differ from that of the unmixed group analyzed. The occasional occurrence of two neoplastic elements in the same tumor is well known to pathologists, and therefore needs no elaboration.

There were five males and two females. Neither nationality nor occupation seemed to play any definite rôle. The age of the patient at the time the tumor appeared varied rom 15 to 39 years. The duration of the lesion before the patient came to the Memorial Hospital varied from five to twenty years, with an average duration of nearly ten years.

For a possible bearing on etiology there might be mentioned one case in which there was irritation of a benign mole by scratching; in a second there was a form of benign lesion that had existed for years which was accidentally incised by a barber, and which on failure to heal was treated with hydrochloric acid; in a third case, the patient sustained a blow which resulted in a "scab" formation, being followed by a lesion that never healed. The remaining four cases had nothing in the least suggestive, and in these there was no preexisting lesion.

Ulceration was present in four cases and absent in three. In four cases that showed ulceration, the process was definitely spontaneous in one, questionably so in two and caused by external agents in the remaining one.

Pain was present in three of the seven cases; it seemed to be relieved by treatment.

In five of the patients the lesion was located on the nose, in one on the eyelid and in the other on the forehead. In five of the cases there was considerable local extension of the disease. In one case the temporal bone was destroyed and the meninges and brain were involved. In two of the cases the disease apparently extended little, if at all.

Only four of the cases have been followed-up for three years or more. Obviously, the number is too small to be of much value. Hence, only a few features will be mentioned.

All of the patients had had previous inadequate treatment with irradiation, and one had also been operated on. At the Memorial Hospital irradiation (external and interstitial) was employed in conjunction with surgical procedures. One patient died of extensive pulmonary tuberculosis (positive roentgenograms and sputum, typical

clinical picture) and was apparently free from carcinoma. The patient with involvement of the meninges was lost from observation after being observed for one year and four months. His case was hopeless from the time of his first appearance at the Memorial Hospital, and he is doubtless dead. One patient is living and seems free from disease (observed for seven years and nine months). The fourth patient is living, but is in poor condition.

To justify the tremendous mortality, one must admit that when the patients arrived at the Memorial Hospital the disease was so extensive that the outlook was already hopeless.

NONCUTANEOUS GROUP

There are twenty-one cases in this group. Two of these have some squamous features and will be analyzed separately.

Table 3 gives in decades the ages at which the lesions were first noticed. Such data were obtainable in thirteen cases. The youngest patient was 35; the oldest, 76. The average age was 50 years.

TABLE 3.—*Age Incidence in Thirteen Cases*

Decade	*Number of Patients*
4th	4
5th	2
6th	6
8th	1

Eleven of the patients were males, and eight were females. This slight preponderance of males may be explained by the fact that more than one half of the lesions in this group were within the mouth, and that in the male syphilis, bad teeth and smoking are more common than in the female.

Etiology was studied in the nineteen cases. In five males and three females there was nothing that would suggest the cause of the disease. In one male and two females there was a possibility of irritation from a dental plate. Trauma was mentioned in the cases of one male and two females. The use of tobacco and the presence of bad teeth were listed in three males. In one female no history on this point was recorded, and in one male a supposed sebaceous cyst had been removed from the nasal end of the lacrimal duct. Thus one can find no definite causal agents for this group of tumors. Cohnheim's theory of embryonal rests, or bits of misplaced tissue, must suffice until further information is elicited.

Occupation and nativity seem to have no bearing on the disease.

Ulceration was definitely present in nine and absent in four of the patients. In six cases there was no definite statement, but five of these probably had ulceration. It was difficult to tell whether or not the ulceration was spontaneous. Many of the patients had had treatments before coming to the Memorial Hospital.

In none of the cases was there any familial history. There was no tendency for any of the lesions to remain stationary or to involute without treatment.

In only four cases was there any definite history of bleeding before treatment. These patients either had a primary lesion of the nose or an extension into that organ.

The detection of a swelling by fifteen of the patients caused them to seek medical advice. One swelling was first detected by a dentist who was caring for the teeth.

In seven of the cases there was localized pain of a steady, dull type. Soreness was complained of by one patient who had a lesion of the mouth and by another who had a swelling of the tongue.

There were no definite preexisting lesions.

As nearly as could be determined, the palate was the primary site in seven of the cases, the antrum in three, the mucosa of the cheek in two, the alveolar ridge in three, the lip in one, the tongue in one and the nose in two.

The disease progressed by direct extension. Those lesions primary in the palate usually entered the nose and antrum. The ones which began in the nose and antrum ordinarily invaded the mouth, orbit and ethmoids. In at least one case the meninges were involved by direct extension into the cranial cavity. The anatomic relations of the parts usually affected make this method of spreading easy and render the tumor dangerous.

In most of the cases there are no data concerning the duration of the lesion before the patients came to the Memorial Hospital.

Fourteen cases have been observed for three years or more, and these are the only ones that will be used in the follow-up study.

Previous treatment consisted of surgical excision in the majority of the cases and irradiation in a few. From this it would seem that the medical profession in general is not aware of the beneficial results that may be obtained from a well executed plan of irradiation therapy. When employed, this treatment should be given as early as possible. This form of treatment is recommended because of the relative radiosensitivity of this group of tumors and on account of the discouraging results obtained from straight surgical measures.

The treatment at the Memorial Hospital consisted of irradiation primarily and surgical intervention secondarily. External applications

(usually radium rather than roentgen ray) were employed in twelve cases. As a general rule, the radium was applied locally over the area of involvement, and if the neck was irradiated, it was customary to utilize the roentgen ray. At the present time, however, there is an increasing use of large radium packs both locally and to the neck. By means of isolated clinical observations it has been thought that this method can be supplemented with the high voltage roentgen ray, thereby giving a larger tumor dose with less injury to the skin than can be given by either form of irradiation separately. It is hoped that results will be improved by this method.

Interstitial irradiation, which usually consisted of radon enclosed in glass tubes (for about the past four years gold tubes have been used), was resorted to in all but three cases. In one of these three the lesion was in the lower lip and could be effectively treated by external irradiation alone. In the other two, the disease was so far out of bounds and was progressing so rapidly that strenuous measures were not deemed justifiable.

Surgical intervention was employed in seven of the fourteen cases. In five of these it consisted in evacuation of the orbit or antrum, sometimes one and at other times both, in order to remove infected or over irradiated tissue. The over irradiation was purposely planned, the neoplasm being used as a radium holder, with the expectation of removing the tumor tissue before it necrosed or became infected. In the case in which there was a lesion on the lip, local excision was sufficient. A submaxillary dissection was performed in the case in which there was a neoplasm of the mucosa of the cheek. The extirpated tissue was negative for tumor growth.

Results show that of the fourteen patients observed for three years or more, five were lost trace of. Of these five, one was followed-up for too short a time to predict permanent results. This was the patient with the lesion on the lip and when last seen there was no evidence of disease. One (primary tumor of the palate) is probably dead. The remaining three patients were followed-up for three and one-half, three and two years, respectively. At the end of this time they were all free from disease and in such excellent condition that one might assume that they are still alive and well. Two of these had primary tumors of the palate, and one had a neoplasm arising from within the nose.

Only two of the patients are definitely known to be alive. One of these, who has been followed-up for four years, had a primary tumor in the mucosa of the cheek. In the group of squamous carcinomas, this site would be regarded with unusual apprehension, for metastases would be expected. When the patient was first seen, the lesion was very extensive and despite previous excision had infiltrated the masseter muscle. The treatment at the Memorial Hospital consisted in cautery

excision of the ulcerating lesion and the application of external and interstitial irradiation. The second patient, who has been followed-up for six and one-half years, exhibited an ulcerating lesion of the soft palate measuring about 3 cm. across. The therapy consisted solely in one insertion of bare tubes into the lesion.

Seven patients are known to have died. Three had primary lesions in the palate; three had lesions originating in the maxillary sinus, and one had a lesion arising from within the nose. The high mortality may be explained by the fact that the patients came late, and the disease was so extensive that there was little hope of even slight palliation. In some, if not all, it seemed that previous ineffective treatment had aggravated the condition.

The duration of treatment and the duration of observation were so often terminated by the death of the patient that no definite conclusions could be drawn from such a study.

Complications were frequent and often severe. In the late stages pain, insomnia, anorexia and asthenia were common. Sequestrums were noted in at least two cases. Infection was frequently the immediate cause of death. In three cases there were signs and symptoms of infection of the central nervous system (meningitis or brain abscess). One patient had acute parotitis.

Conceding that minor histologic differences could be seen in some of the tumor tissue, this feature did not seem sufficiently marked to account for the difference in the mortality.

Mixed Squamous and Adenoid Cystic Basal Cell Carcinomas From Noncutaneous Sites.—In addition to the foregoing nineteen cases there were two that combined a few squamous with the adenoid cystic features. One of the patients had a primary tumor of the palate which apparently developed some squamous characteristics during the course of treatment at the Memorial Hospital. She was under observation for seven years, and there was evidence of local disease at the time of death. Physical signs were suggestive for fluid in the pleural cavity, but autopsy was not performed. The second patient, who had a primary lesion in the nose, has been followed up for eight years, and he seems free from disease. There were several recurrences, all of which yielded promptly to treatment.

HISTOLOGY

The material from the Memorial Hospital consists principally of small pieces of tissue, as is usually taken from biopsies, and, therefore, no gross descriptions can be given. It is believed, however, that macroscopic features are not as important as the clinical observations and consequently would add little of value to what has already been given.

The histologic difference between the *cutaneous* and the *noncutaneous* basal cell tumors in this series is sometimes slight and can be given briefly; otherwise, a single description will suffice for both kinds.

In the tumor found in or near the skin, more of the typical basal cell characteristics are seen, and the surrounding connective tissue is more prominent. In the collection from the Memorial Hospital there are sections that demonstrate the origin from the basal layer of the epidermis, but there are two cases which are likewise observed to be springing from the analogous tissue of the oral mucous membrane. In

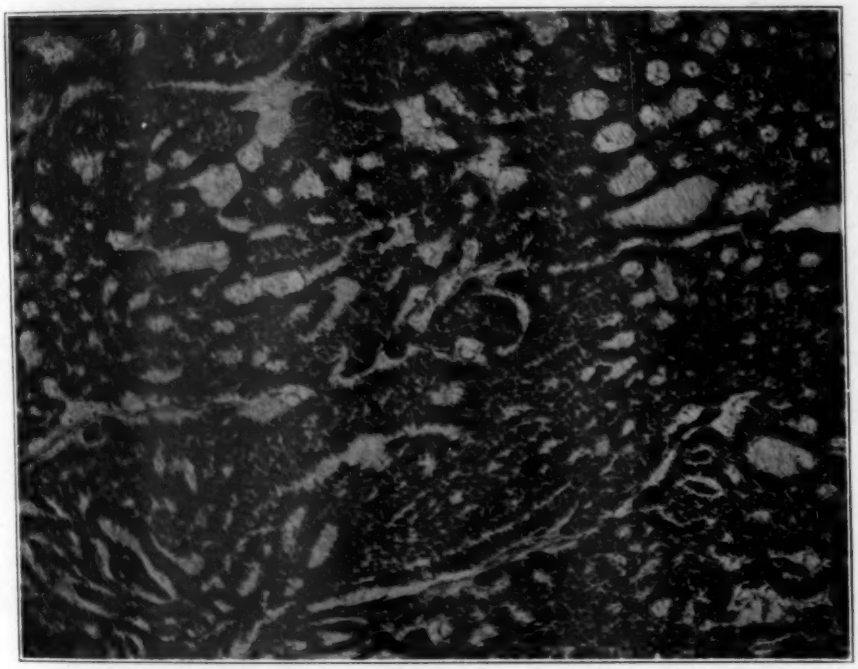

Fig. 1 (cutaneous group).—Primary lesion in the upper eyelid, which had existed for eight years, with a slow, progressive growth. After treatment began the patient had recurrences for two years. For the past five years the patient had been free from disease. The structure is typical for low power.

two of the cutaneous tumors there is distinct production of cartilage, and in other respects these two present the picture of the so-called salivary gland type.

Henceforth, the description applies to both the cutaneous and the noncutaneous types.

Under low power magnification, the tumor cells may be seen in large compact masses, broad sheets, small clumps and strands of varying size or as loosely scattered individual cells. Any of these forms may

exhibit infiltration into the surrounding tissue. The cells on the periphery (more marked in larger masses) often present a palisade arrangement.

Within the tumor cell nest may be observed cysts of varying size and poorly developed adenoid structures (not seen in many), and it is not uncommon to find the cells arranged in a finely interwoven, lacy network. Many of the cystic areas are empty; others are occupied by a smooth, homogeneous substance; these areas are usually contracted,

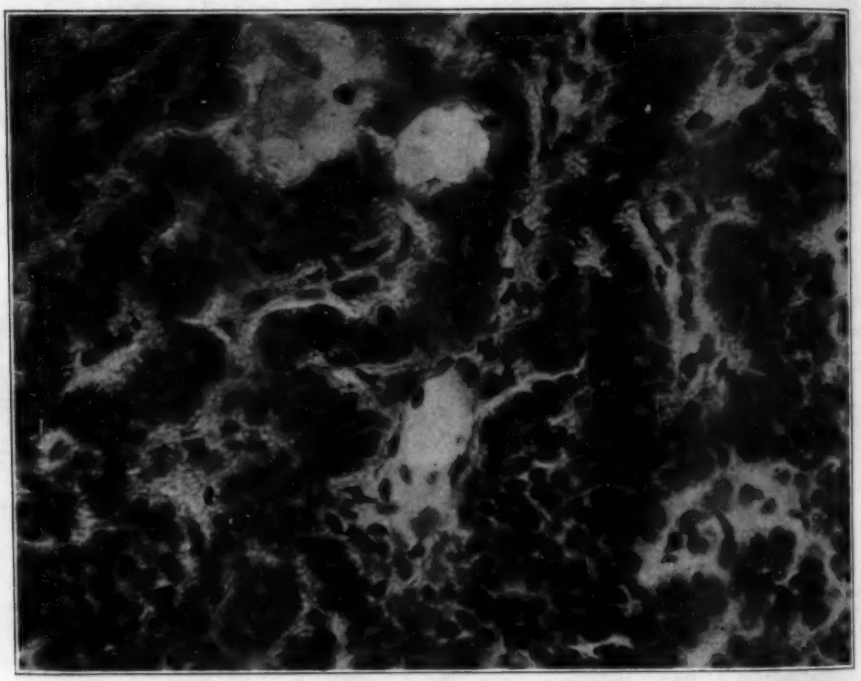

Fig. 2 (cutaneous group).—The patient had a twenty years' history of a small lesion of the skin of the face adjacent to the nose. There was no recurrence during the one year of follow-up study. The same cell type but different arrangement is seen as in the metastases from fatal cases in figures 6 and 9.

leaving a free area adjacent to the tumor cells, and may be due to fixation. The neoplastic cells are moderately hyperchromatic.

Under high power magnification the palisade-like cells often noted on the periphery are clearly seen to be pointing toward the center, where they are closely packed and narrower than elsewhere. The cytoplasm is scanty and is frequently absent. In contradistinction to its appearance under low power, the nucleus now shows clear areas with many uniformly distributed granules of varying size. In some

areas there is a meshy network seen connecting the larger granules. Nucleoli are rare, and mitoses are infrequent. Many of the cells are undergoing dissolution. Ordinarily this process becomes more marked as one leaves the periphery and goes toward the center. At times only a portion of the nucleus can be seen; in some all has disappeared except the nuclear rim. In those cases in which disintegration is complete, or nearly so, the granules that had been in the nucleus may be easily detected lying between cells which are still intact. This tendency toward dissolution can be found in individual cells, but the more striking

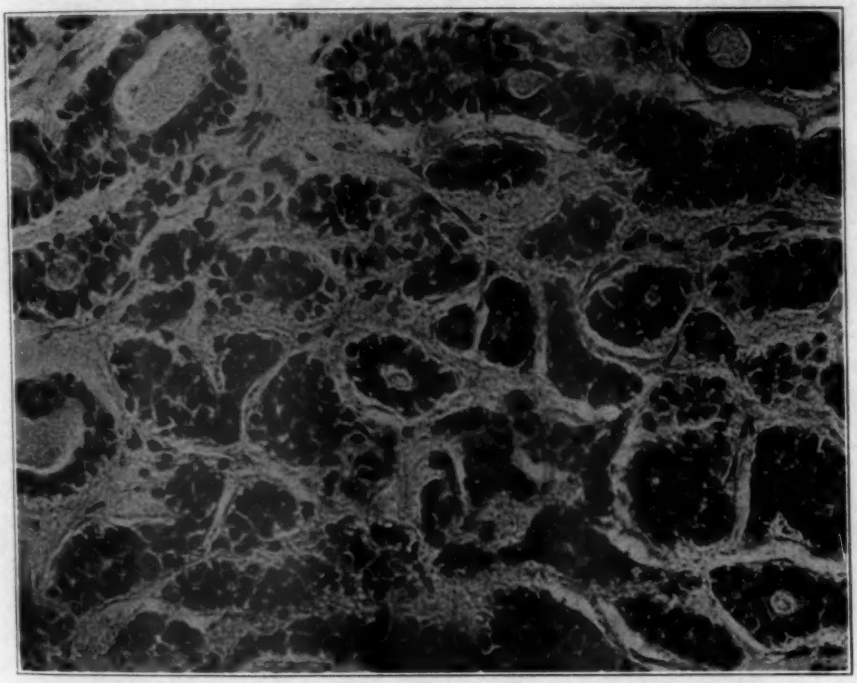

Fig. 3 (noncutaneous group).—Small lump in the soft palate noticed for four months. Regression was complete. The patient was followed-up for six and a half years. The central adenoid spaces are well marked.

examples are those in which small clusters seem to participate simultaneously in the process. In the latter instance the cystic areas are formed, and in the former a granular stroma is seen with here and there the absence of one or more cells.

When the cysts are thus formed, they seem to enlarge progressively by the continuous dissolution of the marginal cells. Thus these centers may become as yawning caverns, continually advancing at the expense of the neoplasms. This process becomes an attack from within, and

one may wonder whether at times the rate of central destruction may thus equal that of peripheral growth. The enlarging cysts may meet others and coalesce with them.

It is easy to conceive that the contents of the cyst may be made up of cellular remnants and débris. Ordinarily this appears as a granular coagulum with occasional interlacing fibrils. In this structure, somewhat as a matrix, there may be embedded portions of partially destroyed tumor cells. Thus it will be seen that what usually appeared as a homo-

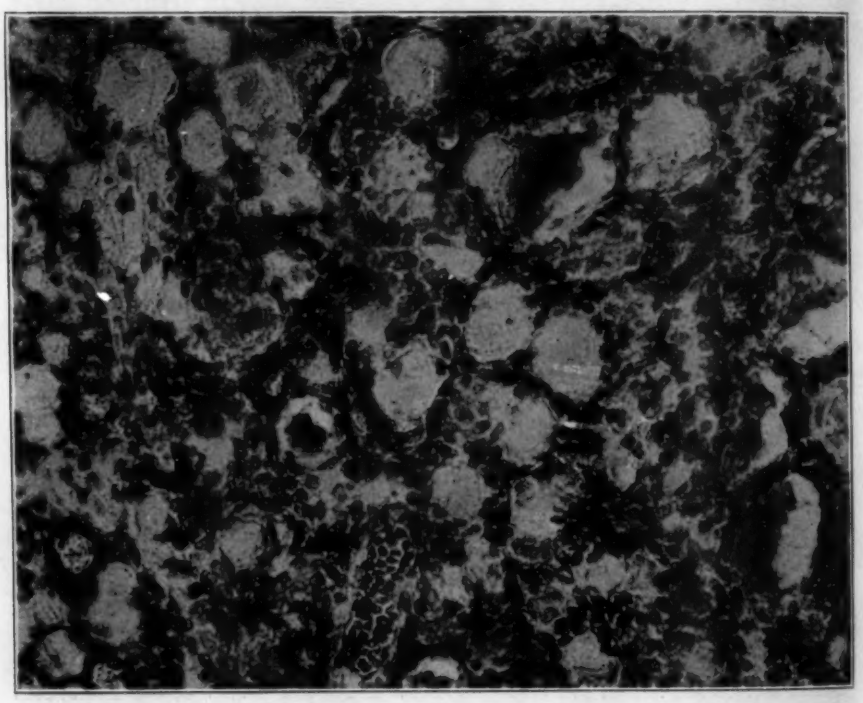

Fig. 4 (noncutaneous group).—The lesion apparently originated in the antrum. Four years' history of epistaxis. The patient died five months after admission with symptoms of meningitis. Autopsy was not performed. The patient probably had an extension backward. The lacy-like network is prominent.

geneous mucoid substance under low magnification may transform itself under high power into a graveyard littered with remains of dead neoplastic elements.

In a few instances the cysts contain a definite hyalinized material resembling that often seen in squamous epithelium. Also it is possible to find areas of connective tissue circumscribed by epithelial tumor cells and in such cases they appear as cystic structures containing connective tissue. These might be termed pseudocysts.

Fig. 5 (case 1).—(Cases with generalized metastases.) The primary tumor of skin near the nose. The enclosure of connective tissue by tumor cells, forming cystlike areas, is demonstrated.

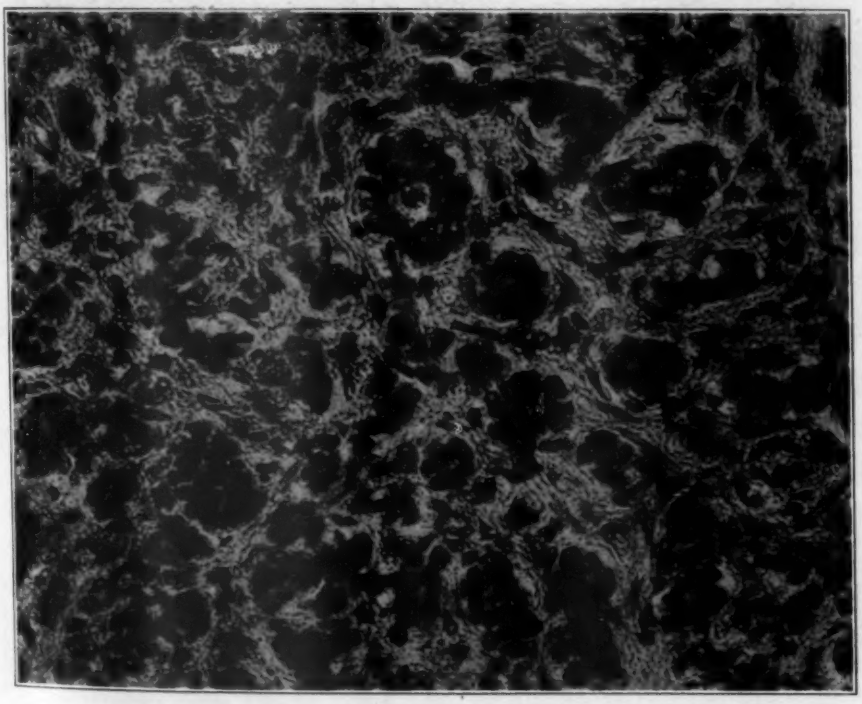

Fig. 6 (case 1).—(Cases with generalized metastases). This shows the metastasis to the spleen. The cells have changed character somewhat but are definitely of the same type, as in figure 5. Cystic areas are not numerous but may be found.

It is not difficult to find some tumors in which the spaces are occupied by a bluish-white substance. In most of these the cysts are poorly formed. It is reasonable to suppose that such a picture could result from the juncture of two or more strands of tumor cells which had thus snared off a bit of connective tissue, and that the subsequent degeneration of the connective tissue could produce a substance resembling mucus. It is doubtful if the cystlike areas contain a true mucoid substance. As far as one is able to determine with the microscope, it would seem that the intracystic material is a product of cellular degener-

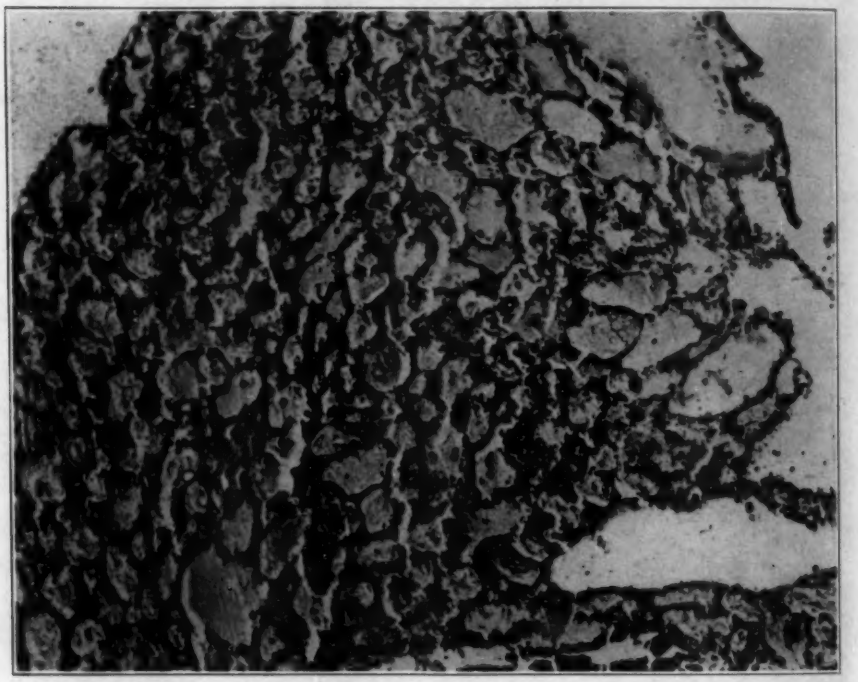

Fig. 7 (case 2).—(Cases with generalized metastases.) The primary (very old section) tumor of the submaxillary area. Note the resemblance to thyroid or to pulmonary tissue seen under low power.

ation rather than of secretion. However, through the kindness of Dr. Alfred Plaut of the Woman's Hospital (New York) I have been able to study the mucicarmine reaction in two cases, premenstrual endometrial tissue being used for a control. The staining reaction thus employed was positive in the adenoid cystic tumors, but it is doubtful if the test is specific enough to differentiate between mucus resulting from cellular activity and colloid material coming from tissue degeneration. For the present it seems wise to leave this point unsettled.

In some tumors there are well formed cysts which may exhibit a distinct membrane. How the latter structure is formed is not definitely determined. The contents of the cysts may have produced it by pressure, the force thus exerted being sufficient to cause condensation of intercellular material. Possibly the action of chemicals in the fixatives and stains may have something to do with it. One cannot say.

In general, the adenoid structures are poorly developed, and one often has to imagine them. In a few sections, however, they seem fairly definite and possess not only an internal but also an external

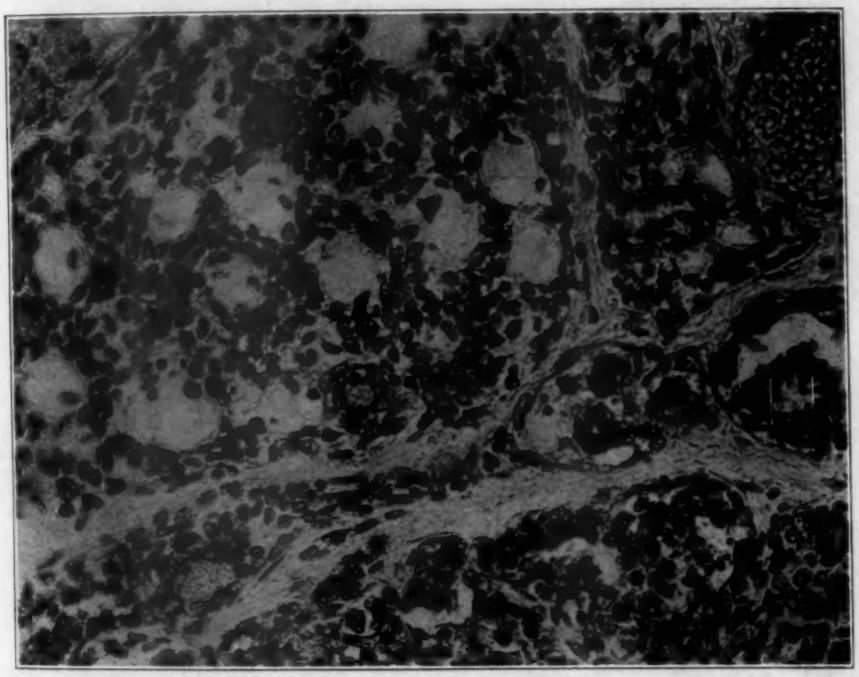

Fig. 8 (case 2).—(Cases with generalized metastases.) The metastasis in the lung from the primary tumor represented in figure 7. The character of the cells has been retained.

limiting membrane, each of which is well formed. But even here the described unit often appears much more like a tubule or duct than a gland proper. In some sections I must confess that I have found the adenoid structures wholly lacking, or else of an indefinite character.

Typically, the stroma is very scanty. A few fibrils with some loose granular bodies may be scattered between the tumor cells. Since most of this is probably a degeneration product of the tumor cells themselves, one can assume that such a structure is hardly comparable to a true stroma. In some instances there is some supporting connective tissue of

the usual sort, but as a rule this is really extraneous and has been infiltrated by tumor cells. In only a very few places is it possible for one to see a fine, closely packed connective tissue which seems to act in the nature of a capsule. The connective tissue seems to be destroyed by the liquefactive properties of the tumor.

Aside from the cartilage formation mentioned, there may be other noteworthy structures. In two sections there have been observed many small, closely packed blood vessels which occupy a considerable portion of the tumor tissue. In these the actively growing neoplastic cells seem

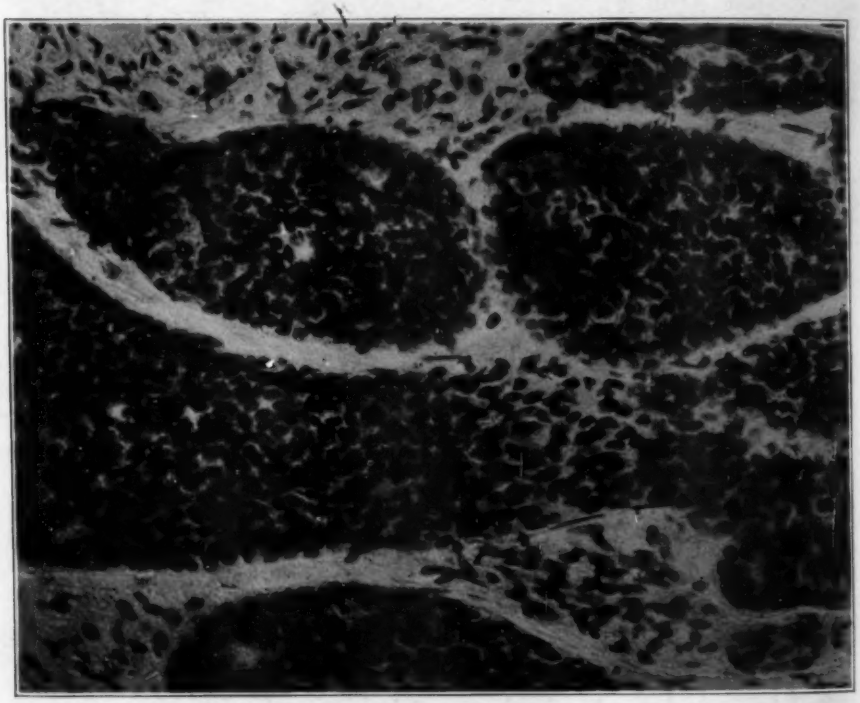

Fig. 9 (case 3).—(Cases with generalized metastases.) The metastatic lesion in the liver. Central degeneration has begun, showing one method by which the cysts are produced. The primary tumor was reported as adenoid cystic epithelioma by a competent pathologist. Some of the general features have undoubtedly changed, but the individual cells are typical and resemble those in figures 2 and 6.

to be infiltrating the walls. They are not altogether typical, however, and it may be that the proliferating cells are from the blood vessels, in which case one may presume that one is dealing with a mixed tumor, an angio-epithelioma, if there is such a tumor. In one section there appears to be hyperplasia of the mucous glands, but this process probably represents an excitation due to the invasion by tumor cells rather than a true neoplastic response.

Fig. 10.—Recurrent nasal tumor; generalized metastases. This illustrates the well marked cystic areas and the general character of the neoplasm.

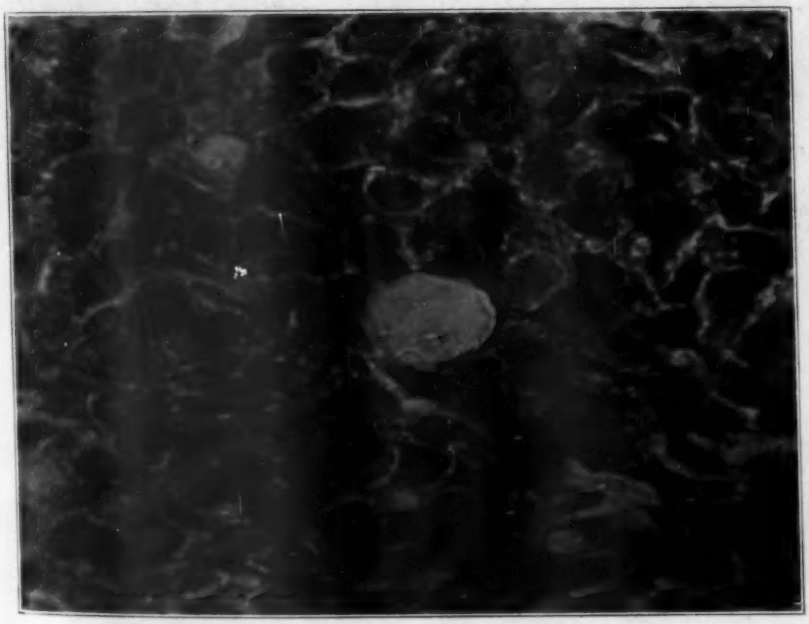

Fig. 11.—A cellular area of figure 10; × 1,300. An early stage of cyst formation and some well preserved cells are depicted.

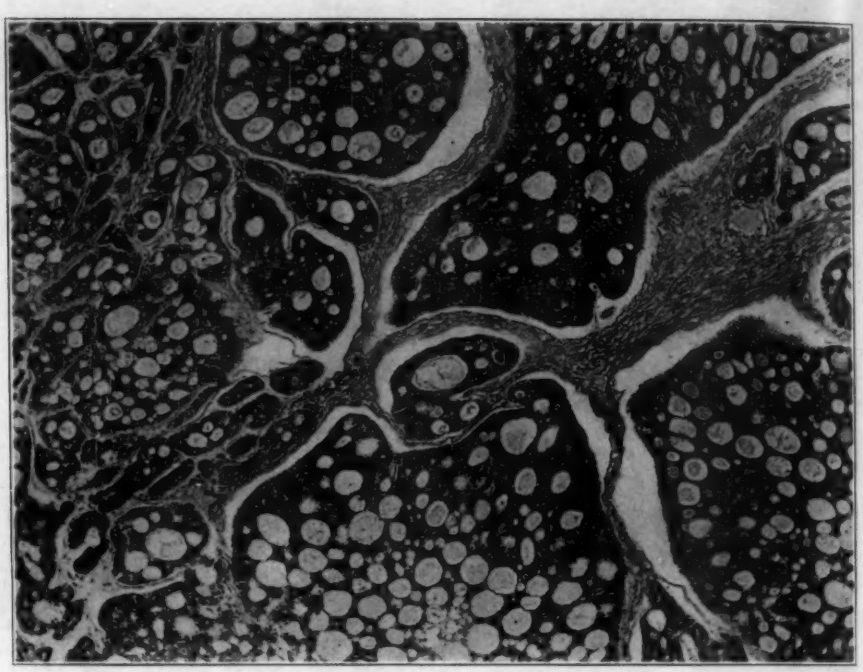

Fig. 12.—Metastatic nodule in the omentum; × 85. The structure is identical with that in figure 10.

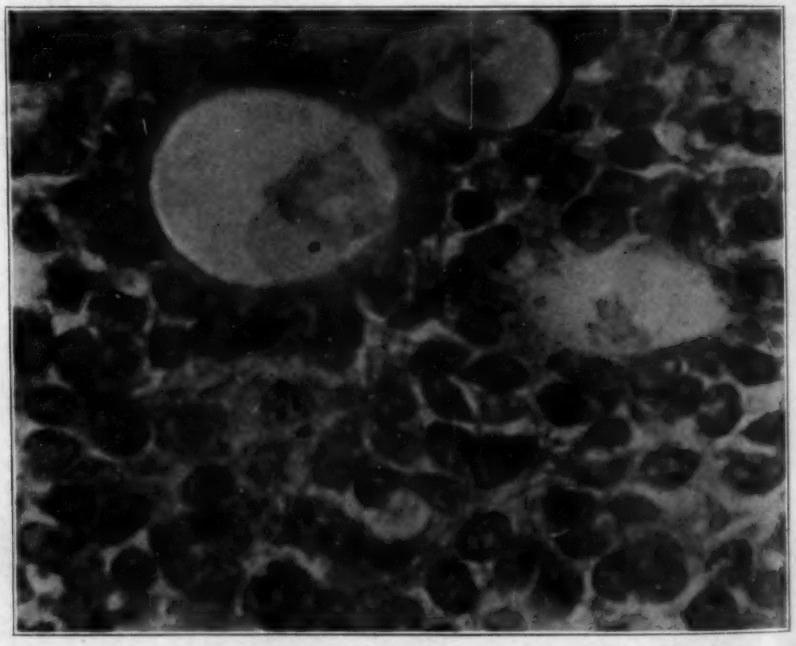

Fig. 13.—A cellular area of figure 12; × 1,300. The degeneration of cells, which seems to precede the formation of the cysts, may be seen.

SUMMARY

In both the *cutaneous* and the *noncutaneous* groups the age of appearance of the lesions, the lack of familial qualities, the tendency to progression without limit and usual presence of ulceration all dispose one to believe that the cases of adenoid cystic carcinoma analyzed should not be classed with the relatively benign skin disorder known as adenoid cystic epithelioma or as Brook's disease. These cases are more closely related to the usual type of basal cell carcinoma (Krompecher), but many do exhibit adenoid and cystic features.

The study of etiology was interesting and slightly suggestive, but nothing more. Sex, occupation and nativity seemed to have little if any bearing on the disease.

The *cutaneous* lesions were situated for the most part on or near the nose or eyelids, while the palate was the most common site for the *noncutaneous* tumors. In the former it was usually the presence of ulceration, and in the latter it was tumefaction, that caused the patient to seek medical advice. The average duration of the skin lesions before the person came to the Memorial Hospital was seven and one-half years. It was impossible to determine accurately this point in the other group.

In the follow-up study, no case was used unless it had been observed for at least three years.

In the *cutaneous* group, fifteen patients were found suitable for such study; twelve had had previous treatment. The treatment usually consisted of the application of salves, but in some cases both surgical intervention and irradiation had been employed either separately or together. Only one patient is known to have died, and the case was obviously hopeless from the start. Recurrences and complications were frequent, but apparently the disease was finally controlled. The average duration of treatment was slightly more than two years.

Mixed basal and squamous carcinomas were found in both cutaneous and noncutaneous groups, but the number of cases was too small to afford more than passing comment. It would seem that the addition of squamous features gives a poorer prognosis.

In the *noncutaneous* group, fourteen cases could be traced for three years or more. In these cases the previous treatment had usually been surgical intervention. At the Memorial Hospital this procedure was used as an adjunct to irradiation. In many of the cases, palliation was all that could be expected. The mortality rate proved to be about 50 per cent. The complications were numerous and severe.

I believe that the great difference in mortality between the two groups cannot be explained on the basis of histology but rather on the fact that in the noncutaneous type the anatomic setting facilitated the

direct extension of the disease into the accessory nasal sinuses and thence even into the cranial cavity. Infection as well as tumor can proceed by the same route and thus dispose of the patient.

Adenoid cystic basal carcinomas are ordinarily radiosensitive, and, as a general rule, the patients should be treated by irradiation (preferably radium) primarily and surgical intervention secondarily.

The histology of these tumors is extremely interesting. The term adenoid cystic carcinoma is explanatory. Many cases lack the glandular features, and in some the cysts are poorly developed. The supporting structure is composed of connective tissue, and in some instances it may contain a substance resembling mucus. The intracystic material is probably the remains of degenerated neoplastic cells and is not a true secretion. The mucicarmine reaction was positive in the only two cases in which it was employed, but it is not believed that it is necessarily specific for mucin.

REPORT OF CASES

There were three cases in which generalized metastases were found. These cases had no squamous features, and their unusual course warrants separate, detailed reports; therefore, they were not included in the foregoing cases. I believe that such widespread dissemination of a basal cell carcinoma has not been reported before, or if so I have not found an account of such. The fact that a basal cell carcinoma may metastasize is given little thought by most physicians, and, although such an extension is rare, one should keep in mind the potential danger of these tumors. In the "adenoid cystic" subdivision of basal cell carcinoma, the possibility of generalized metastases should not be forgotten. It is hoped that the following case reports will justify this statement.

CASE 1.—*History.*—A white man, a clergyman, in 1917, at the age of 58, noticed a "spot" 2 mm. in diameter on the cheek near the right nasolabial fold. It looked like a bit of black dust, was crusted and would not heal. Several months later the lesion was treated with radium. Apparently the lesion disappeared, only to recur two years later, when it was again subjected to an application of radium. The regression was not as satisfactory as on the first occasion. The following year the area was excised and skin grafted. The diagnosis by a competent pathologist was basal cell epithelioma of the face. Three months later a recurrence in the scar was excised.

Following this treatment the patient had four other excisions for recurrences. Each time the diagnosis of basal cell carcinoma was returned. He also received five applications of radium on the edges. Injections of an unknown calcium preparation were given.

Although in 1920 he was treated twice for recurrences in the outpatient department, his first admission to the Memorial Hospital was on July 7, 1927. He stated that for the past five months prior to admission he had had generalized subacute pain in the sternum and ribs. The distress was accentuated by breathing deeply. Three months before admission he had a pathologic frac-

ture of the right clavicle. Several weeks before coming to the Memorial Hospital he was comatose, but recovered fully and promptly. In at least two other institutions of highest rank (in one of which he had been previously treated) the diagnosis of multiple myeloma was made from x-ray pictures. The roentgenograms confirmed the finding of destruction of bone in the spine, ribs, skull, pelvis and other bones. Despite some atypical features in the x-ray films and disregarding the existence of a previous basal cell carcinoma, because they were not thought to metastasize, the provisional diagnosis of multiple myeloma of the bones seemed justified.

Physical Examination.—The patient was well developed and nourished, and intelligent, alert and responsive. The right ala nasi was absent. There was a slight ulceration of the nasal lesion, and the edges were somewhat raised. The lesion appeared to be an unhealed benign process rather than a recurrent epithelioma. Otherwise, the nose was normal. There was a slight protuberance over the right ninth rib anteriorly. The abdomen was soft but slightly distended. The urine occasionally revealed hyaline and granular casts. Examination for Bence-Jones bodies gave negative results. The blood count varied from a hemoglobin of 90 per cent with 4,200,000 red cells on admission to a hemoglobin of 50 per cent with 2,500,000 red cells about two months afterward. Calcium was 15.8 mg. per hundred cubic centimeters of blood. Nucleated red blood cells (one to five) were found in four of the eleven examinations.

Treatment.—(1) A moderate amount of external irradiation with the 4 Gm. radium pack and the high voltage roentgenray was given over the chest and back. (2) A glass bulb (radon) was applied once to the nose. (3) Ultraviolet light was applied on the trunk.

General Course.—While the patient was in the hospital, the general course was slow and progressively downward, characterized by anorexia, malnutrition, mild rise in temperature, slight elevation of pulse rate and gradual diminution in mental power. The patient died on Jan. 5, 1928, at the age of 68, the disease having lasted ten years.

Autopsy.—Marked emaciation was evident. The right ala nasi was missing; the ulcerating tissue appeared neoplastic. There was a marked, lateral, thoracic scoliosis of the right side. There were many rounded tumor nodules in the ribs. Extensive adhesive pleurisy was present on the left side and slight on the right. The heart was small; the muscle was brown, and the right side was distended. The right lung was emphysematous, with a few indurated bronchial thickenings; both lungs suggested neoplastic involvement. The spleen was dotted with miliary nodules. The liver was normal in size, with small nodosities on the superior surface, of the right lobe. The kidneys were small; the capsule was stripped, leaving a granular surface; the cortex was thin. There were numerous adhesions from the omentum to the peritoneum, one of which produced some constriction of the cecum. The urinary bladder was distended with cloudy, purulent looking fluid. The prostate was small and normal. There were calcific deposits in the dura mater; there was edema of the pia mater, and the brain and hypophysis were normal. The skull was honeycombed with numerous fatty-like, partially calcified areas. It was much enlarged and thickened. The same process appeared in the ribs, clavicles, pelvic bones and femora.

Diagnosis.—The anatomic diagnosis (microscopic) was: (1) adenoid cystic basal cell carcinoma arising from the skin of the right cheek, extending into the nose and metastasizing to the dura mater, lungs, spleen, liver and various bones (notably the skull); (2) chronic arterial nephritis; adhesive pleurisy.

CASE 2.—*History.*—The patient was an elderly, white, business man, whose exact age does not appear on the record and who gave no history previous to Nov. 13, 1911. At that time he had a localized, easily shelled out tumor. It was situated near to but was separate from the left submaxillary salivary gland (report from attending surgeon). It seemed to be lying in the subcutaneous tissue. Pathologic examination revealed adenoma with probably commencing cancer.

Treatment.—On July 21, 1913, there were one nodule, the size of a filbert, at the upper part of the old incision, several metastases in the fat tissue and an infiltrating mass extending beneath the mylohyoid muscle backward beneath the great vessels, involving these and the adjacent muscle. The facial artery was thickened. The hypoglossal and glossopharyngeal nerves were saved with difficulty; the branch of the facial nerve going to the mouth was sacrificed. The dissection extended down to the cricoid cartilage (where a soft gland was found) and to the constrictors of the pharynx. The procedure was radical and complete. By pathologic examination, the cells seemed typical of endothelial rather than of epithelial origin. The tumor was pronounced malignant.

During the winter of 1913, the patient froze his face and had considerable irritation of the skin. In May, 1914, one gland was found in the submental triangle and another in the submaxillary space. A thorough dissection was performed. Pathologic examination showed normal lymphoid structure with fat and fibrous tissue, but no new growth.

On Jan. 16, 1916, a fourth operation was performed for recurrence beneath the jaw and another lesion over the lower border of the jaw, external to the mandible. The largest gland was 1 cm. in diameter. Complete dissection was carried out. The tonsils were enlarged so that a tonsillectomy was performed. Gross pathologic examination revealed: the tissue from the neck was 5 by 4 by 2 cm., in which there was a dense nodule 1 cm in diameter. Microscopic examination revealed tubular glandular tissue, and one place infiltrated into the connective tissue. The diagnosis was adenocarcinoma. The rest of the tissue was normal. The tonsils were large but normal with few enlarged crypts.

On June 5, a nodule (just above the hyoid bone) and the digastric muscle were removed, together with the two small nodules along the hypoglossal nerve, which was then sacrificed. Pathologic examination showed: a piece of tissue, the size of the little finger in the midst of which there was a dense infiltrating growth composed of large plexiform masses of small, undifferentiated epithelial cells with a marked tendency to degeneration, forming small ringlike openings. Masses of cells were separated by trabeculae of connective tissue. There were also small solid masses in the adjacent fibrous muscular tissue. The diagnosis was carcinoma not classified.

The patient was treated by the staff of the Memorial Hospital from Oct. 30, 1920, to March 7, 1926. When first seen, he had a nodule in front of the left mastoid process, and there was some bulging in the left tonsillar fossa.

He received seventeen treatments with radium, distributed as follows: neck (four), submaxillary area (four), spine (seven) and chest (two). All of the treatments were external except three to the submaxillary space, which were interstitial. Palliation was slight, and the patient died on March 13, 1926, fifteen years after the first operation.

Autopsy.—The patient was well developed and nourished. Below the left side of the jaw there was a depressed area of scar tissue 10 cm. long, slightly adherent to the mandible. The skin was leathery and the buccal mucous membrane was intact. There were no gross signs of tumor on section. The left tonsillar region was the seat of a firm, leathery, cicatricial mass, 4 cm. in diam-

eter, movable on the deep tissue and adherent to the intact mucosa. There were several minute cysts filled with mucus and some calcific points. No definite tumor was visible. At the level of the base of the tongue was a third mass, 2 cm. across. It was hard and contained many cysts, considerable opaque tumor tissue and numerous blood sinuses. The heart was large, but was otherwise normal. In the visceral pericardium there was a fibrous plaque 3 cm. across. Two hundred centimeters of straw-colored fluid was found in the pleural cavities. The pleurae showed a dense generalized fibrous thickening, and they were the site of flat, cicatrized, centrally depressed tumor masses, averaging from 1 to 3 mm. in diameter. In the lungs were numerous tumor nodules, from 0.5 to 2 cm. in diameter. Some tumor masses appeared densely fibrosed, while others were soft. There was no enlargement of the lymph nodes, congestion or pneumonia. The spleen was slightly enlarged; the follicles were invisible. The liver was of normal size with a few miliary tumor nodules. The suprarenals, stomach, pancreas, bladder and prostate were normal. In the spine there was a slight sharp kyphosis of the fourth and fifth lumbar vertebrae. The right transverse process of the fourth lumbar vertebra was enlarged and the periosteum was thickened. The body of the sacrum, all of the lumbar, the eleventh and the twelfth dorsal vertebrae cut readily with a knife. The osseous tissue was congested and mottled throughout by opaque tumor areas. The remaining bones were not examined.

Diagnosis.—The anatomic diagnosis (microscopic) was: recurrent carcinoma, originating in the left submaxillary space; extension to the left tonsil and base of the tongue; metastases to the lungs, pleurae, liver and spinal column.

Comment.—In the scar tissue below the left side of the jaw were scanty tumor cells which were atrophic and degenerated. The tonsillar mass showed fibrosis and calcification. On the lower edge there were isolated foci of tumor cells which contained widely dilated blood sinuses. In the intermediate nodule at the base of the tongue there was well preserved tumor tissue with many small mucous cysts. The lungs exhibited diffuse fibrosis and degeneration of the tumor cells together with some foci of the large cells with hyperchromatic nuclei. The liver presented active proliferation of the tumor cells, and in the spinal tissue there was alveolar and diffuse carcinoma. Some of the bone-marrow showed a peculiar necrosis.

From the foregoing data, the following conclusions regarding the course of the disease seemed warranted: The tumor in the neck, below the jaw, had been devitalized and rendered quiescent. The tonsillar mass showed living tumor tissue, especially along the lower border, and the usual development of the venules offered a channel through which the disease might have become disseminated. Many of the nodules in the lung probably existed for years and had undergone spontaneous fibrosis. Many others were more recent and were somewhat active. The presence of most of the tumor masses in the wall of the chest rather than in the lung accounted for the absence of pulmonary symptoms. It is possible that the pulmonary metastases occurred several years before examination, but it may be that they began more recently, being transported direct from the vascular areas of tumor tissue in the neck. The main cause of the rapid decline was probably due to the swift course and destructive nature of the lesion in the spinal column. It was difficult to account for the extreme congestion and extensive necrosis of tissue in the spinal vertebrae.

Case 3.—*History.*—A white woman, aged 50, presented herself at the Lexington Clinic, Lexington, Ky., in March, 1928, at which time she said that she had had a nasal discharge for the past two and a half years. There had been three severe nasal hemorrhages, the blood from one of which measured about 2 liters.

Examination.—Examination at the clinic revealed a widening of the bridge of the nose with marked dilatation of the alae nasi. The tumor completely obstructed the right nostril, and the septum was pushed so far to the left that the left nares was also obstructed. The tumor was fungoid and bled easily.

Her general condition was poor, and her hemoglobin was only 35 per cent. X-ray pictures of the lungs revealed several areas that were interpreted as old healed tuberculosis.

Treatment.—At operation, the tumor was found to be confined within the septal mucous membrane, which was degenerated but intact except at the right mucocutaneous junction from which the tumor mass protruded. The mass showed practically no invasion. The entire septum was removed by means of actual cautery, and four days later radium (1,000 milligram hours) was inserted.

Course.—The patient was sent home two weeks after operation. Three months later she returned for examination, and no evidence of disease could be found in the nose. She complained of pain in the abdomen and had a palpable epigastric tumor. It was felt that the tumor might be a metastatic carcinoma, but on account of the diagnosis of basal cell carcinoma, adenoid cystic type which had been correctly returned by one of the country's most eminent pathologists, it seemed that the mass might be something other than a metastatic carcinoma, and exploratory operation was performed. A neoplasm measuring about 8 cm. across was found in the superior surface of the left lobe of the liver. A biopsy was taken and the abdomen closed without further examination.

The patient was sent home and has been observed several times since. A report on May 11, 1929, from Dr. E. C. Yates of the Lexington Clinic stated that: X-ray pictures of the skull were negative. Roentgen examination of the chest showed several metastatic areas, and in the right upper end of the humerus was an area of destruction due to metastases. The spine, pelvis, hips and both femurs were negative for metastases. The patient had a large tumor mass in the abdomen and had a considerable amount of pain intermittently. The patient's general condition, however, looked good. She showed a secondary anemia; urinalysis gave negative results. The local area in the nose showed no gross evidence of recurrence, but there were two small nodules in the external canthus of the right eye and one larger nodule near the left lower alar cartilage. On Oct. 31, 1929, Dr. Yates wrote: The patient had metastases to the right humerus; the remainder of the bony skeleton was intact. She also had metastases throughout her entire abdomen and her chest.

Autopsy.—The body was that of an extremely emaciated white woman about 53 years of age. The abdomen was markedly distended, and the superficial blood vessels were prominent on the right side. A small, firm, nodular tumor was present just below the inner canthus of the right eye. Numerous, small, brown, slightly raised areas were in the skin over the side of the chest and abdomen. The peritoneal cavity contained about 8 liters of clear, amber-colored fluid. There was about 30 cc. of blood-tinged fluid in the right pleural cavity. The left lung was studded with firm, grayish nodules that varied from 1 to 40 mm. in diameter. The posterior portion of the upper lobe was replaced by a large mass of this firm tissue. The right lung was essentially the same as the left, but the right pleural cavity contained no fluid. The ribs were the seat of extensive metastases, being more marked on the right where the sixth and seventh ribs exhibited pathologic fractures posteriorly. Grossly, the vertebrae were negative, and the head of the right femur was involved. The heart was normal. The mediastinal lymph nodes were slightly enlarged. The liver was tremendous, and was occupied by a large tumor mass and a few smaller ones. Sections through the

neoplastic tissue revealed many minute cavities and a few large spaces filled with clear fluid. The gallbladder was not unusual. The stomach was distended with gas an was closely adherent to the under surface of the liver. The inferior surface of the diaphragm was spotted with numerous, grayish-white plaques, and this condition existed throughout the peritoneum. The spleen was surrounded by firm adhesions but was not enlarged. A few small gray tumors were in the capsule and substance of this organ. The kidneys were normal, except for dilatation of the pelves. The ureters were distended. The suprarenals showed no gross lesions. The omentum, mesentery, ovaries and fallopian tubes were masses of tumor tissue. The uterus was normal. The meninges and brain were normal. In the right side of the nose (posterior, superior and lateral portion) there was a pedunculated, friable tumor 3 cm. in diameter.

Histology.—Sections from the tumor in the nose revealed a basal cell carcinoma enclosing numerous small and large cysts which contained a pale staining mucoid material. The histologic structure of the tumors in the lungs, liver, peritoneum, omentum, ovaries, fallopian tubes and the ribs was identical to that of the nasal neoplasm.

Diagnosis.—The anatomic diagnosis was: primary adenoid cystic basal cell carcinoma of the nose with extensive generalized metastases.

SUMMARY

In the first case the tumor apparently originated in the skin of the cheek near the right nasolabial fold. It ran a slow course for years, remaining localized, but finally destroyed the right ala nasi. Recurrences were persistent despite the efforts of roentgenologists and surgeons. Without any increase in the activity of the local tumor there was widespread metastases to the bones and viscera. This dramatic change was confused with multiple myeloma, for it was thought that the basal cell nature of the tumor of the skin precluded its metastasis.

Possibly the primary site of the neoplasm in the second case was in the submaxillary salivary gland, but it was thought to be separate from it. The lesion was early suspected of being an adenocarcinoma and was thoroughly operated on several times. The progress of the malady was slow but steady. Irradiation was enlisted as a last resort, and the local effect seemed beneficial, but the dissemination was wide and distant.

The mucous membrane of the nasal septum gave rise to the carcinoma in the third case. The patient did not present herself for treatment until she had had severe hemorrhages and almost complete nasal obstruction. Soon after that she had a palpable tumor in the epigastrium which proved to be metastasis, and the x-ray films revealed areas of increased density in the pulmonary fields. This patient is still living and has shown favorable effects from the treatment (surgical intervention, locally, irradiation there and to the metastases), but undoubtedly she is doomed. This case differs from the other two in sex, slightly younger age and lack of treatment until the disease was advanced.

In each of the three cases the tumor originated in supposedly different tissues, but they presented a somewhat similar histologic structure.

It is realized that the tumors may conceivably have begun in misplaced bits of tissue thus following out the Cohnheim theory, but this assumption does not seem warranted.

CONCLUSIONS

1. Adenoid cystic carcinoma is probably a distinct disease and should not be confused with adenoid cystic epithelioma as described by Brooke and Fordyce and should be regarded as different from adenocarcinoma.

2. There are two general groups, both being based on whether the tumors arises from a *cutaneous* or a *noncutaneous* site. This grouping is justified by the low mortality in the former as compared to the high death rate in the latter.

3. The histologic structure in the *cutaneous* and the *noncutaneous* groups is similar, and in each it closely resembles that of adenoid cystic epithelioma of Brooke and Fordyce. The cystic form of rodent ulcer is likewise confusing, and histologically may be identical with the cutaneous type of adenoid cystic basal cell carcinoma. In the *noncutaneous* tumors one must rule out adenocarcinomas and so-called mixed tumors of the salivary glands. The history and physical observations are important aids in making the differential diagnosis in each type.

4. Adenoid cystic basal cell carcinoma is a radiosensitive tumor and should be treated primarily with irradiation and only secondarily with surgical procedures. One should not temporize; the therapy should be applied early and vigorously.

5. Although there are well authenticated but rare cases in the literature in which ordinary basal cell carcinomas have extended to the regional lymph nodes, I have failed to find instances in which there were any proved distant or generalized metastases. That such widespread dissemination may occur is believed to be reported here for the first time. It is this feature that I particularly wish to emphasize.

NOTE.—Since the compilation of the data in this article, there have been several cases in which the invasion of bone by "adenoid cystic basal cell carcinoma" has occurred. This ability of this type of tumor to metastasize to bones is upheld in a case report recorded by Martin.[52]

Most of the material came from the service of Dr. Douglas Quick. Dr. E. C. Yates, Lexington Clinic, Lexington, Ky., supplied data on one of the most important cases. Dr. Alfred Plaut of the Woman's Hospital, New York, stained some of the material for mucin. The photographs were supplied by Mr. William Dunn.

52. Martin, Hayes E.: Adenoid Cystic Epithelioma of Scalp, with Dissemination to Bones, Bull. Memorial Hospital **3**:46, 1929.

TOPOGRAPHIC RELATIONSHIP BETWEEN THE NERVE PLEXUSES AND LYMPH NODES OF THE ABDOMEN *

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SZEGED, HUNGARY

The standard anatomic texts, such as those of Gray,[1] Bardeleben and Haeckel,[2] Poirier,[3] and Testut,[4] as well as the monographs of Müller,[5] Bartels,[6] Hovelacque [7] and others, give exact descriptions of the topography of the abdominal nerve plexuses and the abdominal lymph nodes. Up to the present, however, there has been no description of the topographic relations between the two systems. Clinical experience teaches that metastases and inflammatory processes in the abdominal lymph nodes cause various symptoms, such as pain and functional disturbances in various organs. Further, it has been seen that after operative removal of such nodes severe postoperative complications, such as paralysis and trophic disturbances, often occur. The purpose of this paper is to give a topographic-anatomic explanation for these phenomena. My studies concerning this question are all made on human material, and my illustrations in the text were also derived from the same source. In general, I have chosen for my observations cadavers (those of children and adults) in which the abdominal lymph nodes were somewhat enlarged. In preparing my specimens I used most of the modern methods,[8] such as dissection under water, digestion with acidol-pepsin, etc. Fresh or partially preserved material may with great advantage be kept in running water from fourteen to sixteen days during the process of dissection. By this means the connective tissue becomes edematous and remains soft, while the lymph nodes and nerve fibers retain their original consistency.

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* Submitted for publication, Feb. 27, 1930.

1. Gray: Anatomy, Philadelphia, Lea & Febiger, 1918.
2. Bardeleben and Haeckel: Atlas der topographischen Anatomie, Jena, Gustav Fischer, 1908.
3. Poirier, P.: Traité d'anatomie humaine Paris, Masson & Cie, 1901.
4. Testut: Traité d'anatomie, Paris, Gaston Doin, 1911-1912.
5. Müller, L. R.: Das vegetative Nervensystem, Berlin, Julius Springer, 1920.
6. Bartels: Das Lymphgefäss-system, in Bardeleben: Handbuch der Anatomie, 1909.
7. Hovelacque, A.: Anatomie des nerfs craniens et rachidiens et du system grand sympathique, Paris, 1927.
8. As described in a monograph by Worobiew: Methodik der Untersuchungen von Nervenelementen des makro- und makro-mikroskopischen Gebietes, Berlin, Oscar Rothacker, 1927, pt. 1.

In the following description, I shall discuss the topographic relationship of the separated lymph node groups to the nerve plexuses. In the nomenclature of the nerve plexuses, I shall use the classification that I have published in collaboration with Ballon.[9]

The cardiac or paracardial lymph nodes lie in the immediate vicinity of the vagus nerves (Jamieson and Dobson[10]). The left group of

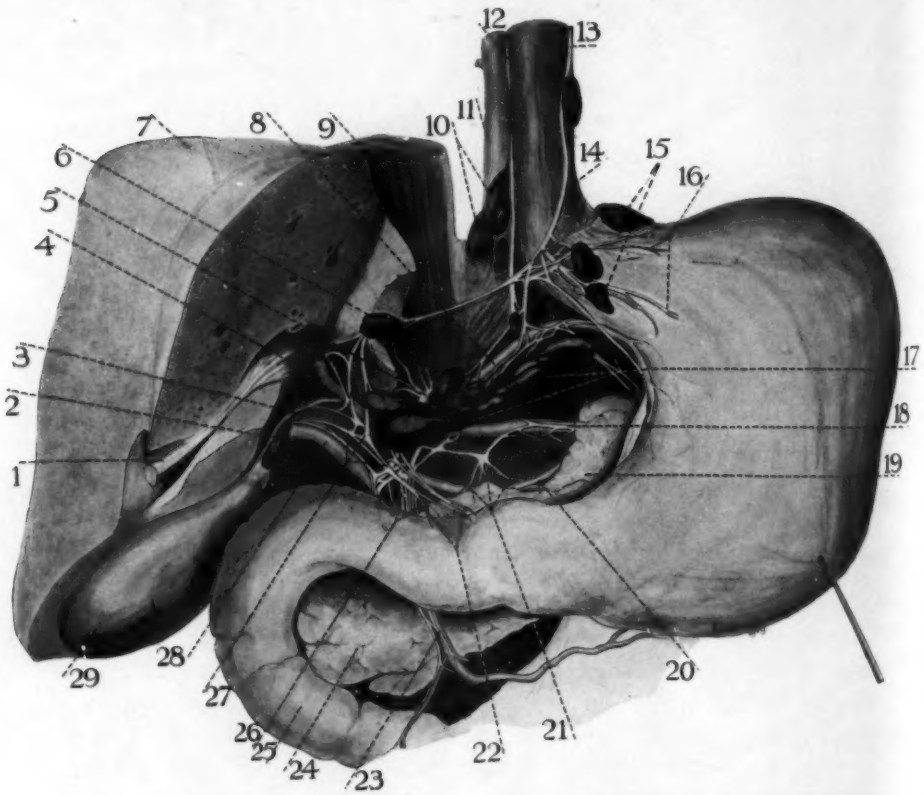

Fig. 1.—This figure and figures 2, 3 and 4 show the topographic relationship between the nerve plexuses and the lymph nodes of the abdomen. Here *1* indicates round ligament; *2*, cystic node; *3*, cystic artery; *4*, hepatic artery; *5*, right celiac ganglion; *6*, hepatic node; *7*, liver; *8*, left gastric artery; *9*, lumbar part of the diaphragm; *10*, paracardial nodes; *11*, aorta; *12*, right vagus; *13*, left vagus; *14*, esophagus; *15*, paracardial nodes; *16*, cardiac branches of the vagus; *17*, superior gastric nodes; *18*, splenic artery and plexus; *19*, pancreas; *20*, splenic vein; *21*, pancreatic plexus; *22*, pyloric plexus; *23*, gastroduodenal artery with nerves; *24*, head of pancreas; *25*, duodenum; *26*, pancreatic plexus; *27*, hepatic plexus; *28*, common duct; *29*, gallbladder.

9. Kiss, F., and Ballon, H. C.: The Celiac Plexus and Its Branches, Arch. Surg. **19**:399 (Sept.) 1929.

10. Jamieson and Dobson, in Poirier (footnote 3).

these nodes lies directly on the gastric branches of the left vagus which run along the anterior surface and both curvatures of the stomach (fig. 1). Hence even the trunks of the vagi can be influenced by these nodes.

The upper gastric nodes (lymphoglandulae gastricae superiores) form a chain around the left gastric artery. This artery is accompanied in its course by two large branches of the vagi, one from each vagus, in addition to other small gastric branches that take part in the formation of the celiac plexus. These are the parasympathetic (vagus) roots of the celiac plexus which supplies most of the abdominal organs, such as the liver, pancreas, kidneys, suprarenals and intestine. Whether these fibers have specific cells in the celiac ganglions or merely traverse these ganglions and have their ganglion cells only in the respective organs is still an undecided question. For my observations it is important only to know that these branches are exposed to compression or irritation from inflamed (enlarged) lymph nodes. In the operative removal of the lymph nodes, injury of these important nerves is inevitable.

One group of these nodes, the right group, lies in the hepatoduodenal ligament in front of the portal structures immediately over the fine branches of the hepatic plexus. These nodes are called the hepatic lymph nodes (fig. 1). They lie in the loose connective tissue of the hepatoduodenal ligament in close relationship, on the one hand, to the portal structures such as the hepatic artery, the portal vein and the common duct, and, on the other hand, to the fine nerve branches of the hepatic plexus. As Ballon and I have shown in the aforementioned publication, the branches of the hepatic plexus are exposed to manifold injuries in operations on the biliary passages. As figure 1 clearly shows, this plexus can also be greatly influenced by pathologic changes in the hepatic lymph nodes. Radical removal of the nodes can result in destruction of the greater part of the plexus. Since the lesser curvature of the stomach in the living lies much nearer to the hilus of the liver than is shown in figure 1, the branches of the pyloric plexus, the gastroduodenal plexus and the pancreatic plexus (fig. 1) lie in the immediate vicinity of the hepatic nodes. The cystic node (fig. 1) lies on the cystic duct, where it comes in contact with the cystic artery and the cystic branches of the hepatic plexus. If the duodenum and the head of the pancreas are grasped and these structures are pulled to the left (figs. 2 and 3), important topographic relationships are seen between nerves, lymph nodes and ganglions. The posterior pancreatic nodes are seen lying on the head of the pancreas with the nerves to the head of the pancreas (figs. 2 and 3). Three nodes in the vicinity of the duodenojejunal flexure lie in close connection with the origin of the large superior mesenteric plexus (figs. 2 and 3). On the posterior abdominal

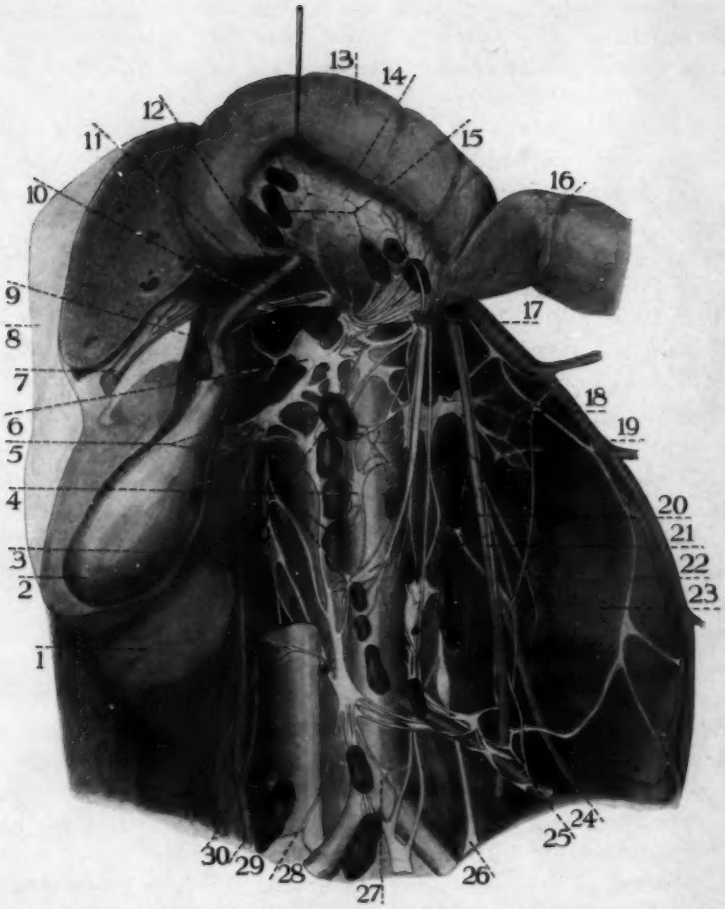

Fig. 2.—In this figure, *1* indicates the kidney; *2*, gallbladder; *3*, right sympathetic cord with retroperitoneal lymph nodes; *4*, aortic plexus with aortic lymph nodes; *5*, renal plexus; *6*, right celiac ganglion; *7*, round ligament; *8*, liver; *9*, cystic artery and lymph node; *10*, celiac lymph nodes; *11*, common duct; *12*, portal vein with hepatic plexus; *13*, duodenum (posterior surface); *14*, pancreas; *15*, posterior pancreatic lymph nodes; *16*, jejunum; *17*, superior mesenteric plexus; *18*, left renal plexus; *19*, left colic vein; *20*, left aortic lymph nodes; *21*, internal spermatic vessels with nerves; *22*, nerve to the descending colon; *23*, left kidney; *24*, sigmoid vein; *25*, inferior mesenteric artery and plexus; *26*, left sympathetic cord; *27*, aorta with aortic plexus; *28*, inferior vena cava; *29*, ureter; *30*, right colic veins.

wall to the right of the aorta, the right celiac ganglion—a flat, soft structure—lies in the retroperitoneal connective tissue. Immediately on its anterior surface are two or three large lymph nodes (the celiac lymph nodes, figs. 2 and 3). The ganglions as well as the lymph nodes in the living are covered by the head of the pancreas and the deep pancreatic nodes. It can clearly be seen from my specimens that the celiac ganglion can easily be influenced by various pathologic changes in the aforementioned nodes. Since the celiac ganglion is to be con-

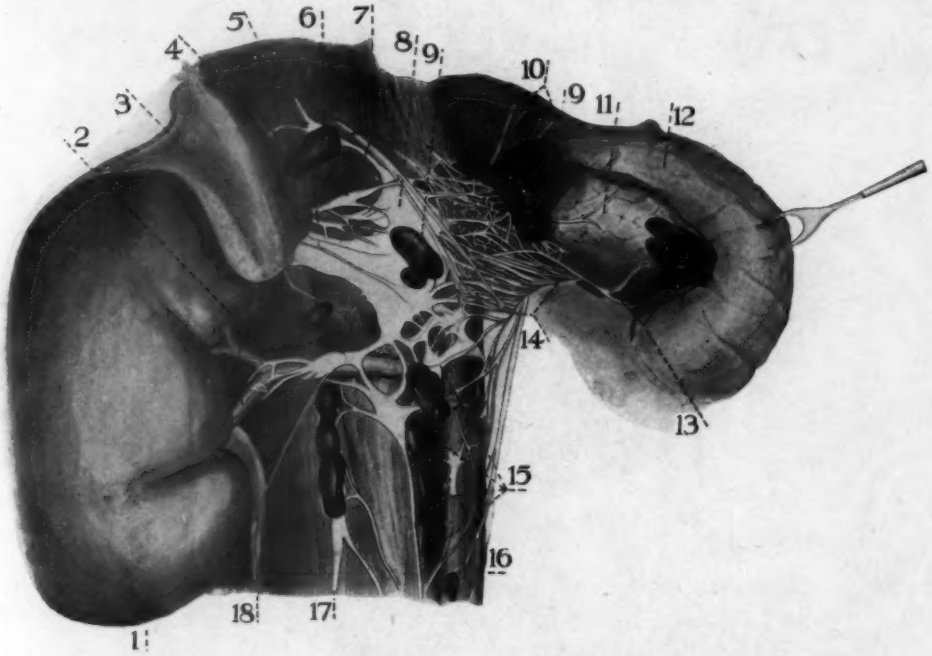

Fig. 3.—In this figure, *1* indicates the right kidney; *2*, renal artery with plexus; *3*, suprarenal body; *4*, suprarenal plexus; *5*, phrenic ganglion; *6*, suprarenal lymph node; *7*, diaphragmatic plexus; *8*, celiac ganglion; *9*, celiac lymph nodes; *10*, hepatic plexus; *11*, head of pancreas; *12*, duodenum (posterior surface); *13*, posterior pancreatic nodes; *14*, superior mesenteric plexus; *15*, aortic plexus with aortic nodes; *16*, aorta; *17*, sympathetic cord with lymph nodes; *18*, ureter.

sidered as a topographic and also partly as a physiologic center of the abdominal plexuses, it is clear that irritative stimuli of this ganglion can be referred to all abdominal organs. Figure 4 shows that the branches of the superior mesenteric plexus in the mesentery lie in close relationship to many other lymph nodes. From a topographic standpoint, however, the aforementioned pancreatic nodes as well as the celiac nodes seem to be fare more important, because by influencing

the celiac ganglion and the main roots of the entire superior mesenteric plexus, they can influence the greater part of the intestines.

Figures 2 and 3 show the huge aortic plexus with the numerous aortic lymph nodes. All of these structures lie in the retroperitoneal connective tissue on either side of the aorta. Smaller and larger nerves as well as the ganglions lie in close relationship to the lymph nodes.

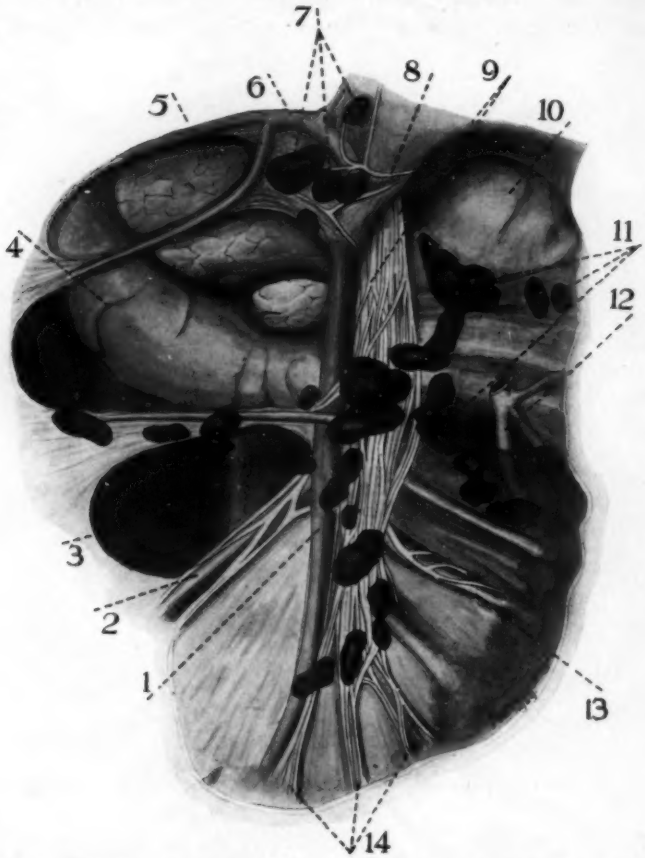

Fig. 4.—In this figure *1* indicates the superior mesenteric vein; *2*, branch of superior mesenteric artery with nerve; *3*, inferior vena cava; *4*, duodenum; *5*, pancreas; *6*, middle colic vein; *7*, mesenteric lymph nodes; *8*, nerve to the transverse colon; *9*, superior mesenteric plexus; *10*, duodenojejunal flexure; *11*, middle mesenteric lymph nodes; *12*, left colic vein; *13*, branch of superior mesenteric artery with nerves; *14*, branches of the superior mesenteric artery and plexus (to the small intestines).

Since the dissection of the complicated nerves and lymph nodes requires a most painstaking technic, it can be readily understood that the ordinary operative removal of these nodes is accompanied in every case by

appreciable injury of the nerves and ganglions. A topographic study of these structures explains the various preoperative and postoperative complications of the lymph nodes, such as referred pains, functional and trophic organic disturbances, etc. For a clear understanding of this question one must not forget that all of these nerve plexuses contain fibers from the sympathetic, parasympathetic (vagus) and spinal nerves (sensory) and probably also special trophic fibers. These separate fibers are influenced separately or simultaneously by pathologic changes in the lymph nodes.

The renal nerve plexus (figs. 2 and 3) also is closely related to several lymph nodes (renal nodes).

Figure 2 shows the origin of the inferior mesenteric plexus with the one lymph node among the nerve fibers. Since the number of the lymph nodes varies in different persons, a greater number of nodes may be found in a special case than any of the foregoing illustrations have shown.

Figure 3 further shows the suprarenal and the diaphragmatic plexuses which also are closely related to the nodes shown in figures 1 and 2.

The superior mesenteric plexus in the radix mesenterii surrounds the trunk and the branches of the superior mesenteric artery (fig. 4). As figure 4 shows, innumerable mesenteric nodes lie directly on the nerve fibers, and some are even between the fibers.

SUMMARY

1. The abdominal lymph nodes lie in close topographic connection with the ganglions and nerve plexuses.

2. Pathologic changes in the lymph nodes, such as hyperemia and enlargement, may cause various nervous symptoms, such as irritation, paresis, etc.

3. The ordinary operative removal of diseased lymph nodes may result in various injuries to the nerves and ganglions. This explains various postoperative complications after such operative procedures.

THE ETIOLOGY OF NEOPLASMS OF THE BREAST

WITH NOTES ON THEIR RELATION TO OTHER TUMORS OF THE REPRODUCTIVE SYSTEM *

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NEW YORK

Special Aspects of the Physiology and Histology of the Normal Breast
The Ovary's Influence on the Physiology of the Breast
The Ovary's Effect on the Histology of the Breast
Special Characteristics and Relationship of Pathologic Growth Processes in the Breast
Theories of Eugen Albrecht on the Organoid Nature of Tumors
The Architecture of Tumors in Relation to Etiology
The Relation of Breast Neoplasms to Those of Allied Organs
The Supposed Causes of Origin of These Tumors of Allied Organs
The Cause of Certain Semineoplastic Growth Processes in the Breast
Experimental Evidence on the Nature of the Cause of Tumors of the Breast
Previous Views on the Origin of Tumors of the Breast
Clinical Study
Classification
Age Incidence
Degree of Breast Development
Previous Breast Disease
Abnormalities of Ovarian Function
Associated Pelvic Disease
Associated Thyroid Disease
Physical Examination of the Breast
Notes on General Physical Constitution
Heredity
Histologic Form of Cancer of the Breast in Relation to Etiology
Résumé

My purpose in this paper is to examine the evidence in support of the theory that a functional disturbance of the physiologic relationship between the ovary and the breast is an important factor in the genesis of many forms of tumor of the breast.

Since the literature on mammary neoplasms already contains the reports of many scattered observations and a few definite studies that favor such a contention, an important part of the present undertaking must be the coordination of some of the recorded material into what is hoped may be a logical conception.

The histologic aspect of neoplasms of the breast has received the attention of the pathologists of several generations so that it appears

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* From the Memorial Hospital.

unlikely that much further progress can be made at present by means of morphologic studies. For this reason, I will be content with previously described and for the most part accepted pathologic structures and will concern myself only with the attempt to correlate these structures with the physiologic conditions under which they occur.

The clinical approach to the etiologic problem has also received much attention, but such studies made with a constant regard for the precepts of breast physiology have been few and imperfect. Yet the correlation of special disturbance of function with particular deviations in form may well be at the root of the tumor problem, and until more exact methods have been devised, the abnormalities of breast physiology are best discovered by the clinical history of its past performance and the determination of its physical condition and that of its associated organs.

The view that specific physiologic disturbances are concerned in the production of tumors suggests at once that many errors may have been made by students of mammary neoplasms on account of a prejudice in favor of the irritative agents that have been satisfactorily demonstrated as predisposing to cancer in other organs and a scant regard for the physiologic differences inherent in the breast cells. The result of comparing the tumors of the breast with those of other organs can be made to lead to quite different conclusions. The tissue which evolves cancer most definitely in response to external irritation is squamous epithelium, whose normal function of the protection of underlying soft parts is evoked by this type of stimulus. The epithelioma can therefore be regarded as the result of an excessive reaction to the specific stimulus to which the squamous epithelial cell is physiologically best adapted to respond. If such a conception is correct, one must look for a different type of stimulus for the tumors that arise from the glandular tissues of the breast.

This study of the evidence leading to the belief that an endocrine disturbance is an important factor in the causation of tumors of the breast is presented in the following form:

1. A consideration of the stimulus which normally produces proliferation in the breast shows that it is the ovarian secretion to which the breast cell is specifically responsive throughout life.

2. A consideration of the changing histologic structure of the breast shows that many of the pictures incidental to a normal response of the parenchyma of the breast to the ovarian secretion differ only slightly from that of certain neoplastic processes.

3. Attention is drawn to the fact, illustrated particularly by the work of Eugen Albrecht, that tumors resemble organs both as regard their structure and their behavior, and very likely their origin.

4. An analogy is offered between the tumors of the breast and those of the other parenchymatous organs of the reproductory system. For many of these

tumors an ovarian dysfunction has been suggested as causative; for a few it is nearly proved and has displaced an older inflammatory theory.

5. The evidence is given to show that certain hypertrophies and hyperplasias of the breast that lie on the borderline between physiologic and neoplastic growth are probably dependent on ovarian dysfunction.

6. A few of the features of the biology of tumors of the breast in animals and their behavior under experimental conditions, are cited mainly in support of an internal causative factor.

7. The chief previous theories of origin of fibro-adenoma, "chronic mastitis" and carcinoma are discussed.

8. A clinical study of 271 cases of mammary tumors is offered as a preliminary survey of the field of ovarian disturbance in relation to the genesis of tumors of the breast.

SPECIAL ASPECTS OF THE PHYSIOLOGY AND HISTOLOGY OF THE NORMAL BREAST

THE OVARY'S INFLUENCE ON THE PHYSIOLOGY OF THE BREAST

In the study of the causes of abnormal cell growth in the breast, it is essential to consider first the stimuli that produce normal cell growth, or, to place the emphasis more correctly, the stimuli to which the cells of the breast are physiologically adapted to respond.

The modern theories in regard to the physiology of the breast were formulated by Josef Halban in a study published in 1905. In this work, based chiefly on an extraordinary array of clinical facts and observations, he came to the conclusion that the ovary was the cause of breast growth except during pregnancy, when the placenta performed this function, but that secretion was a totally different process and was due to the loss of the growth stimulus and was actually the beginning of involution.

Halban's conception of the life history of the breast's activity is that of a long wave extending from birth through puberty and maturity to the menopause with secondary waves, superimposed on it, the latter being the cyclical periods of premenstrual activity and the irregularly placed waves of pregnancy and lactation. The physiology of these phases of breast development shows clearly the conditions favorable to the proliferation of breast cells.

(*A*) *Breast Activity in the Prenatal and Neonatal Periods.*—Swelling and secretion of the breasts is observable in the majority of newly born children of both sexes (Lindig, Hoeland). For many years it has been believed that the cause of this infantile breast secretion must be nearly identical with that of the simultaneous maternal mammary activity (Knoepfelmacher). This view was amplified by Halban's studies of the breasts of premature stillborn infants which showed that there was some proliferation intra-utero as early as the eighth or ninth lunar month. This fetal breast activity Halban ascribed to the effects

of "the pregnancy substance" reaching the fetus through the placenta. In spite of some dissent (Lindig), there seems little reason to doubt that this postnatal secretion affords the earliest example of a proliferative response of the breast to a hormonic stimulation. This view has received important support from a very recent study of Philipp, demonstrating a folliculin-like substance in the blood and urine of newly born children.

(*B*) *Breast Development at Puberty.*—That the development of the breast at puberty is dependent on the presence of an active ovary has long been indicated from the failure of the breasts to develop in women with infantile or absent ovaries and in animals castrated before breast growth has occurred.

Positive evidence of the dependence of the breast on the ovary for its development has been given by two types of experimental procedure —organ transplantation and the use of organ extracts. The earlier work with transplantation was performed by Knauer, in 1900, and Halban, in 1903, both of whom found that the reimplantation of ovaries in castrated animals resulted in a new development of the mammary gland. Later, Steinach and Athias were able to produce breast growth even in male guinea-pigs by this method. The production of hyperplasia of mammary glands in castrated and later in immature animals in response to various extracts of the ovary and placenta has been accomplished by many workers, among whom may be mentioned Frank and Unger in 1911, Fellner in 1913, Herrmann in 1915, and more recently Steinach and Laqueur with their co-workers.

The determination of the special structure within the ovary from which arises the substance that produces the breast growth at puberty is of theoretical interest only in the present clinical study (Steinach, Lipschütz, Allen and Doisy). On the other hand, it is essential to note the apparent physiologic state of the sexual function under which breast growth occurs. The studies of Stratz and of Weissenberg have shown that there are slight indications of breast growth in the tenth year, and that by the fifteenth, when practically all girls have well developed breasts, still one third have not menstruated. It should therefore be clear that the fully developed follicle-corpus luteum apparatus is not essential either to the initiation of breast growth or to its considerable development and it is in fact an intermediary stage of ovarian activity, before menstruation has become established, that is most favorable to the proliferation of breast tissue.

(*C*) *The Menstrual Activity of the Breast.*—The participation of the breast to some extent in the changes of the menstrual cycle is indicated clinically from the consideration of the many women who complain of premenstrual sensations in their breasts, such as pain,

tenderness and at times moderate enlargement. There are even instances, such as the case reported by Schweitzer, of a definite cyclical period of milk secretion at the time of the menstrual flow.

Studies in the field of animal experimentation indicate also that there is a definite influence exerted on the breast by the corpus luteum. Bouin and Ancel were able to demonstrate this on the rabbit by observing hypertrophy of the breast in association with artificial corpora lutea produced by mating a virgin female with a sterilized male. Other authors, including Frank and Unger, O'Donoghue, Hammond and Marshall, and Loeb and Hesselberg, made similar observations on mammary gland growth in relation to the formation of corpora lutea. It has, of course, been repeatedly demonstrated that in several animals proliferation of breast tissue follows the injection of corpus luteum extracts.

To correlate these observations with the normal condition in the human breast it is only necessary to point out that several studies (Frank and Goldberger, Hirsch) have demonstrated a rise in the ovarian hormone content of the blood from the time of ovulation at the middle of the intermenstrual period to the onset of menstruation at which time a rapid disappearance takes place. This period of relatively high hormone concentration in the circulation corresponds with the time of corpus luteum growth and the clinical signs of premenstrual breast activity. Finally, histologic changes confirm the existence of a monthly cycle in the breast.

(*D*) *The Breast Development During Pregnancy.*—It has usually been considered necessary to divide the activity of the breast during pregnancy into two phases, that of proliferation and secretion or of preparation and function, and most authors have recognized that an essential difference must exist between the causes of these fundamentally separate processes.

(1) Proliferation Phase: Halban thought that the placenta was the cause of proliferation during pregnancy, and, except for its neglect of the part played by the corpus luteum in the early months of pregnancy, his theory remains valid today.

(2) Secretion Phase: Lactation is apparently the result of the cessation of a preceding stimulus to proliferation for it is known to occur after parturition, after abortion and after delivery of an hydatidiform mole, and microscopic evidence of slight secretion is found after the onset of menstruation (Ernst, Moszkowicz). That the placental activity is antagonistic to the breast's function was proved by Frankl when he prevented lactation in mice by means of placental transplants. Since secretion occurs only when the stimulus to proliferation ceases, some authors have regarded lactation as a kind of physiologic cellular degeneration or beginning involution (Hildebrandt).

Not only at the onset of lactation but throughout its course are there evidences of antagonism between breast function and placental or ovarian activity. This antagonism is illustrated most dramatically by the observed disappearance of the milk supply under the influence of a new pregnancy but it has also been shown (St. Engel) that in women whose breasts have been secreting insufficiently, menstruation (ovulation) returns in the first few months post partum. Cohn has observed an increase in milk secretion in a puerperal woman on whom bilateral oophorectomy was performed for osteomalacia. Keller referred to similar results following castration in cattle. Inversely, Parkes and Bellerby, working on mice, believed that they could obtain a diminution in the milk supply by the injection of estrus-producing hormone.

The effect of the ovary on the clinical course of lactation must, therefore, be great, and this must be borne in mind in interpreting various points in the lactation histories in cases of cancer. Postpartum engorgement of the breast may be the result of excessive hypertrophy and as such have no inflammatory significance. A short nursing period due to defective milk supply is dependent on a developmental anomaly or on early return of ovulation and is not proof that there has been chronic irritation from stasis of secretion. Even puerperal mastitis or "caked breast" may be in part due to some internal stimulation, for in such a case observed at the Memorial Hospital Clinic rapid improvement followed with the onset of the impending menstrual period.

(*E*) *Breast Activity at the Menopause.*—The cessation of ovarian activity is accompanied in the breast by a gradual atrophy of the parenchyma and its replacement by fat and fibrous tissue. Yet certain reservations must be noted.

The disappearance of ovulation as manifested by the menstrual periods is frequently very irregular. Such irregularities when due to special abnormalities of ovulation have been related to endometrial hyperplasia and are perhaps equally related to hyperplasias of the breast.

After the cessation of menstruation, it is probable that slight ovarian activity continues for a time from the cells of the atretic follicles or related structures. There is thus again for a short time a condition of partial ovarian activity as there was at puberty when breast growth is so marked.

Finally, in rare cases there may be a late return of menstruation or at least a pathologic condition of the ovary having the ability to affect the endometrium (Schiffmann, Meyer).

Summary of Notes on Physiology.—1. The hormone of the ovary or placenta is the agent to which the parenchyma of the breast is normally adapted to respond with proliferation.

2. The effect of the ovary is felt by the breast from before puberty until after the menopause, but it is especially during the periods of partial activity when there is no menstrual cycle (prepuberty, pregnancy) that the greatest hypertrophy occurs.

3. Breast secretion is apparently a passive phase and evidence only of a preceding stimulation that has partly or completely disappeared.

THE OVARY'S EFFECT ON THE HISTOLOGY OF THE BREAST

A study of the histology of the normal breast, particularly in its various phases of activity, reveals many structural forms that are found also in certain neoplastic diseases of the breast and points to a semiphysiologic basis for the latter.

(*A*) *Histology of the Breasts in the New-Born.*—The histologic similarity of this early physiologic hyperplasia to that of the abnormal hyperplasias of later life has been particularly emphasized by Cheatle, and indeed many of the structures present in "chronic mastitis" have their counterparts in the infantile breast. Dietrich's recent studies show that in newly born children the breasts contain hypertrophied glands with a two-layered epithelium surrounded by a loose connective tissue partially differentiated from the supporting stroma. Evidences of secretion in the form of fat droplets are present in the lumina of the ducts and in the epithelial cells (Hoeland). Round cell infiltration is mentioned by many writers (Berka), but since it parallels the secretory function it is usually regarded as a resorptive mechanism. Finally, it is interesting to note that Dietrich observed two cases of microscopic cyst formation which he regarded as the result of an incomplete involution following this infantile lactation.

(*B*) *The Histology of the Breast in Relation to Puberty.*—The histologic changes at puberty consist in a marked increase in parenchyma with the differentiation about the epithelial elements of a specialized loose connective tissue, variously known as periacinar or mantle tissue (Berka). An island of glands with its stroma is known sometimes as a lobule or by many German authors as a "gland field." Aside from this primary growth of epithelial and connective tissue, there are again at times signs of secretion in the breast, and Cheatle noted a temporary return of the lymphocytes.

The rapidity of this growth at puberty and the degree of development attained shows marked individual variations, and Dieckmann has demonstrated that the microscopic structure of the breasts of women of the same age shows great differences in the complexity of the duct and gland systems. Such differences are important for they probably account in part for the clinically observable variations in the response of the mammary glands of different women to the stimuli of the menstrual cycle and pregnancy.

(C) *The Histologic Effect of the Menstrual Cycle on the Breast.*—The first histologic studies on the relation of the human breast to the sex cycle were published by Rosenburg in 1922. This work was based on the examinations of breast tissue obtained at autopsy and correlated with the phase of the sexual cycle as determined by the history of the time of the previous menstruation, by the apparent age of the most

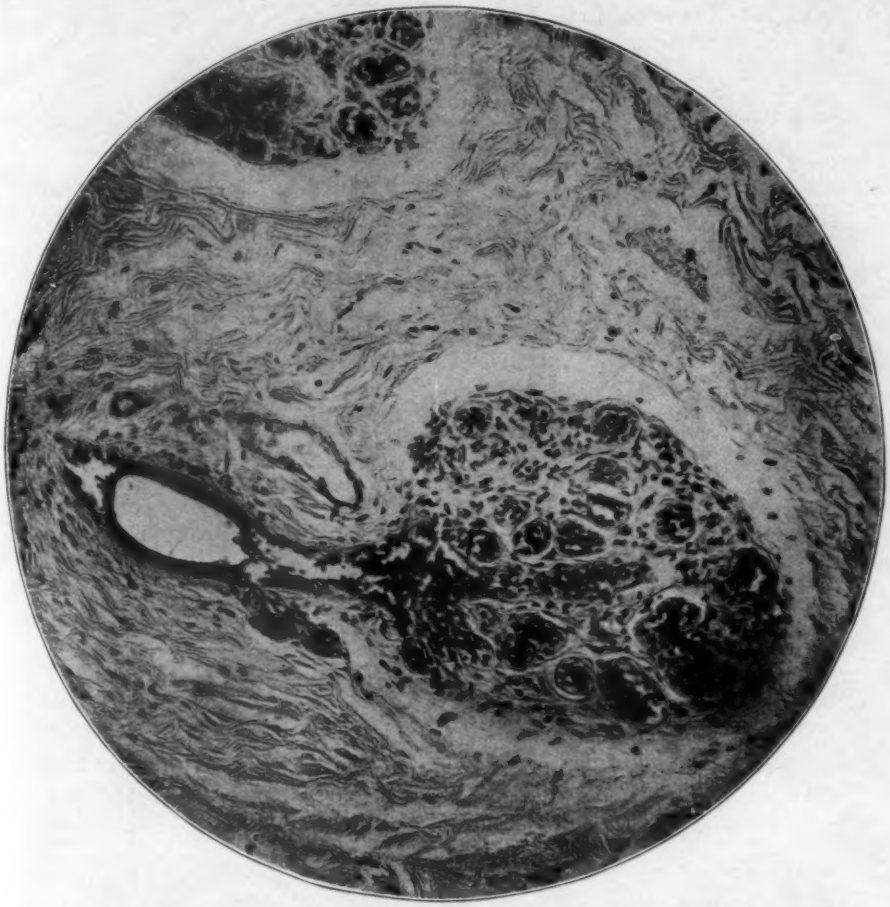

Fig. 1.—Premenstrual hypertrophy of the breast; typical gland field; magnification × 125. (After Rosenburg: Frankfurt. Ztschr. f. Path., Munich [J. F. Bergmann] **27**:466 1922.)

recent corpus luteum and by the examination of the endometrium. His conclusions indicated an actual sprouting of the milk ducts during the premenstruum and an almost complete regression in the interval so that at that time only milk ducts existed in the breast (figs. 1 and 2). Rosenburg definitely ascribed the premenstrual proliferation to the corpus luteum.

Rosenburg's work received a certain degree of confirmation from the studies of several writers (Polano, Ernst, Berberich and Jaffé), but there has also been strong opposition. Dieckmann was able to find little evidence of epithelial change and noted only a premenstrual loosening up of the mantle tissue and a lobular edema, resulting in a more striking demarcation of the gland fields. Moszkowicz agreed

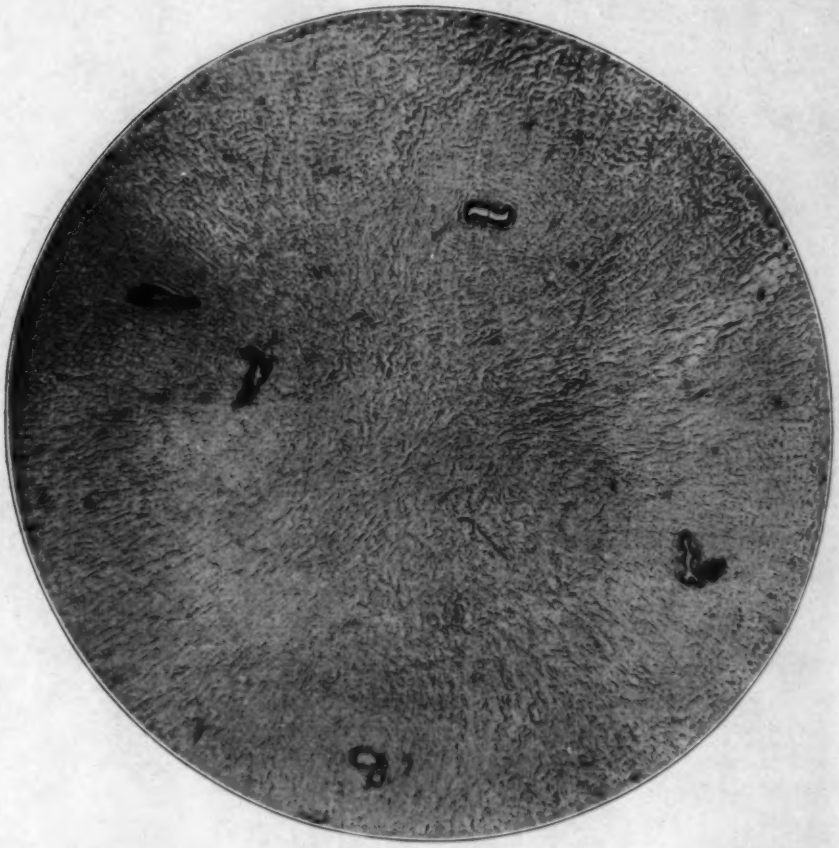

Fig. 2.—Breast in the interval stage; magnification × 18. (After Rosenburg: Frankfurt. Ztschr. f. Path., Munich [J. F. Bergmann) **27**:466, 1922.)

with Dieckmann in finding no direct evidence of epithelial growth but stated as his opinion that some such growth might nevertheless occur and that the actual completion of breast development after puberty might take place during this monthly period of stimulation from the corpus luteum.

The existence of a functional as well as a proliferative phase of activity was emphasized by the studies of Ernst and Moszkowicz. The

former observed that during the menstruum and post menstruum there occurred an infiltration of lymphocytes and plasma cells into the periductal and periacinar tissue that corresponded to the infiltration of cells into the tissues of puerperal women in whom there was stagnation of the breast secretion. He concluded, therefore, that these cells had a resorptive function. Moszkowicz confirmed this recurrent cyclical invasion of round cells and stressed also the occurrence of a definite although transitory fat secretion from the epithelial cells, a process which reached its height during the time of the uterine flow.

The important question of whether an actual proliferation of breast epithelium occurs each month must be considered undecided although the weight of recorded evidence seems now to be slightly against it. There remains the possibility that such extreme degrees of activity occur only in the special type of women who suffer from severe premenstrual breast symptoms. There is some histologic evidence to support such a view for Sebening, in studying the tissues lying adjacent to twelve localized tumors removed for the complaint of "painful nodule," reported that although complete regression in the interval was never observed as Rosenburg had claimed, there was, on the other hand, invariably evidence of epithelial sprouting during the premenstruum.

(*D*) *The Histologic Changes in the Breast Incidental to the Stimuli of Pregnancy and Lactation.*—The development of the breast during pregnancy is described by Berka as consisting of two stages. In the first half of pregnancy there is a rapid proliferation of the epithelium in solid budlike processes that later differentiate into acini. Simultaneously, there is an increase in the mantle tissue which at this period is very cellular and packed with lymphocytes and plasma cells. In the latter half of pregnancy the epithelium takes the form of definite dilated alveoli. The connective tissue is pushed aside and the cellular infiltration largely disappears (Berka). After parturition there is a great increase in the gross size of the gland, but it is doubtful if new acini are actually formed in the puerperium (Berka).

At the end of the nursing period, three histologic processes become apparent: (1) the collapse of the acini with shrinkage and then degeneration of the epithelium; (2) a new proliferation of the periductal tissue (McFarland); (3) a new lymphoid invasion (Berka). The latter process was especially studied by Gruber, who observed the round cells in all breasts in which there was stasis, and construed their function, as Ernst later did for the lymphoid cells incidental to the menstrual phase in the breast, as having to do with the removal of cell débris and secretion.

An interference in this normal process of involution was considered by McFarland to have much to do with the production of the condition known as chronic cystic mastitis, since he considered the cystic structures in this disease to be what he termed "residual lactation acini." It is not quite clear to me whether or not McFarland chose to bind himself to the theory that all multiple cystic conditions in the breast were due to a previous pregnancy. Such a contention is untenable. It has already been pointed out that Dietrich found cystic dilatation in the breasts of infants. Askanazy referred to several instances of cystic breasts in children, in girls at puberty and even in males. The many causes of hyperplasia and even of breast secretion make it seem more plausible to suggest that such cystic dilatations may be the "residual acini" of a previous hyperplasia of some type, whether pathologic or physiologic, but not necessarily of a fully developed lactation.

(*E*) *The Histologic State of the Breast in the Menopause.*—It appears probable that in only a few breasts is the normal course of gradual parenchymatous atrophy followed continuously after the menopause. Instead, several writers who have studied supposedly normal breasts have reported a considerable percentage with signs of irregular epithelial proliferation. Those signs of growth commonly met with, according to Berka, are the multiplication of the cell layers, a subdivision of lumina of glands by anastomosing cords of epithelial cells and the final filling up of the lumina of the ducts with solid masses. Tietze reported such changes in 25 per cent of grossly normal breasts, and Goens found atypical growth in twenty of sixty breasts at autopsy on a series of women over 40 years of age. Such changes as those noted by these authors in the breasts of the older women are, of course, identical with some of the histologic changes in cases of so-called chronic mastitis. The vital question to be asked is whether, after the menopause, one is to discard the type of stimulus that throughout life has caused proliferation of breast tissue and for these older breasts find an entirely new agent.

Summary of Notes on Histology.—1. Epithelial proliferation occurs under physiologic conditions in response to an ovarian or placental stimulation.

2. Connective tissue changes are coordinated with the glandular and are either dependent on an epithelial control or result from similar intrinsic causes.

3. Evidences of secretory activity appear invariably after the cessation of a proliferative stimulus.

4. Round cell infiltration, as a rule, accompanies secretion and is to be regarded as a physiologic resorptive mechanism.

5. Cystic dilatation may be the result of incomplete involution from several types of hyperplasia.

SPECIAL CHARACTERISTICS AND RELATIONSHIPS OF PATHOLOGIC GROWTH PROCESSES IN THE BREAST

THEORIES OF EUGEN ALBRECHT ON THE ORGANOID NATURE OF TUMORS

Before passing to the discussion of the causes of pathologic growth processes, it is necessary in transition to emphasize the close relation between development of normal tissue and neoplastic growth. The theories of the nature of tumors propounded by one writer twenty or more years ago give such an excellent basis for this point of view that they deserve special attention.

Eugen Albrecht, in his papers on "Die Grundprobleme der Geschwulstlehre," stressed organization as the essential characteristic of tumors. It is this quality which demonstrates the relation of neoplasms to organs and distinguishes them from simple cellular multiplication. Benign and malignant tumors differ only in the degree in which they manifest this quality, for some organization, as for example, vascularization, is seen in the least differentiated new growths. Furthermore, the chief characteristic of malignancy, namely, the tendency to infiltrative growth is, as Ribbert had also pointed out, merely the faithful reproduction of the invasion by embryonic cells of the undifferentiated matrix in the course of formation of the earliest anlagen of organs.

Such an "organoid" conception of neoplasms, Albrecht believed, makes the investigation of tumors a branch of the study of the mechanism of development, and therefore, in searching for the origin of new growths, one may consult those laws which bring about the formation of normal organs in the course of normal development. As a result of this point of view, Albrecht recommended the following procedure: first, the analysis of the architecture of the particular tumor; second, the study of the relation of the growth to the organ from which its originating cells must have sprung; finally, by the comparison of its function and structure with those of the normal organ, to draw from the nature of the abnormality conclusions on the causes which may have led to it.

This was an ambitious program and can be followed only in part. It has been shown in the physiologic section that all normal development of the breast was dependent on variations in the ovarian function, and the attempt will be made to indicate that new growths of the breast, as "organoid" structures, are largely dependent on a similar stimulus.

THE ARCHITECTURE OF TUMORS IN RELATION TO ETIOLOGY

The conventional system of classification of tumors has been evolved chiefly with the view of defining types of clinical behavior. Such a system is not entirely satisfactory for an etiologic study, for it tends to isolate special tumor forms and thus conceals the points of relationship between different neoplasms.

The following may be mentioned as among the more important of the factors which cause variations in tumor architecture and which are of quite unequal importance so far as an etiologic classification is concerned: (1) localization or diffusion of the process; (2) functional state of the tumor cells, and (3) degree of differentiation of the tumor cells. It must not, of course, be imagined that these factors are not interrelated.

The factor of degree of localization is recognized in the separation of benign neoplastic processes into adenomas and hyperplasias. It is a justifiable division etiologically in so far that one must recognize a difference in the localization of the predisposition or of the action of the exciting agent. Yet there is a fundamental similarity, for each form represents a new growth of a tissue characteristic of the organ from which it arises and each exhibits similar potentialities for continued growth or evolution. Furthermore, there are many transitional forms and the localized and diffuse processes may occur in association, as in the breast where microscopic adenomatous nodules may be found developing in areas of chronic mastitis (Bloodgood).

Evidences of functional activity and associated signs of regression or degeneration account for many differences in tumor form that bear little or no relation to the ultimate cause of their origin. That the ratio of connective to glandular tissue in the fibro-epithelial tumors of the breast may be dependent on an entirely physiologic factor is suggested by several cases cited by Deaver and McFarland which led them to the conclusion that a "pure adenoma" was merely a fibro-adenoma in a state of lactation hypertrophy. In Cheatle's case of "pure adenoma" there is no suggestion of a preceding pregnancy, but in the case of a growth so highly organic in structure as the fibro-adenoma there may be other physiologic stimuli capable of secondarily influencing its structure.

To a somewhat different category belongs the development of cysts, the presence of which often dominates the anatomic picture of a tumor but which appear frequently to be due to a disturbance in drainage or absorption coupled with a continuation of the function of secretion and thus to have little actually to do with the neoplastic process itself.

The customary division of tumors into benign and malignant has been developed from a study of morphology in relation to clinical

results, and hence is based essentially on the criterion of prognosis. Such a division has not necessarily any significance from an etiologic standpoint. The recent histologic studies on the varying grades of malignancy in cancer have demonstrated that the adenoma malignum, of the endometrium, for example, is far more similar structurally to an active hyperplasia than it is to the diffusely growing carcinomas of grade III with which it is somewhat arbitrarily associated since both are called "cancer." Yet on account of the existence of this gradual transition in form, from the clearly benign to the definitely malignant, it appears unlikely that, at the point of cellular maturity where clinical malignancy begins, a new biologic process has its inception or an entirely new provocative factor becomes operative.

From the considerations of the foregoing paragraphs it appears that all of the fibro-epithelial neoplasms of the breast may be looked on as representatives of the same basic process, varying quantitatively from each other in respect to several special factors. The study of the origin of special tumor forms becomes, therefore, not a search for the separate causes of several entities, but an examination of the factors causing a tendency of tissues to approach one or the other morphologic extreme. With this reservation, it is useful, however, to recognize three type forms, the localized benign tumors, diffuse hyperplasias and carcinomas.

THE RELATION OF BREAST NEOPLASMS TO THOSE OF ALLIED ORGANS

The suggestion has been made that in the study of the origin of tumors of the breast special consideration must be given to the ovarian secretion, because it is to this agent that the breast is normally responsive. The breast, however, is only one of a group of organs the hypertrophies of which are under the control of the sexual function. A survey of the theories of origin of the tumors arising in these other organs related to reproduction affords a valuable check on the study of the breast, for it appears probable that an exciting agent of at least the same general type must be a factor in the production of neoplasms throughout the group.

The reasons for believing that, in respect to the tumor problem, one may regard the breast, the endometrium, the ovary, the thyroid and the prostate as forming an ill defined group are as follows:

(*A*) There is a similarity of the physiologic causes of hypertrophy in these organs.

(1) *Uterus.*—It is in the endometrium that the greatest similarity to the parenchyma of the breast is noted, for this tissue shows activity at the time of birth (Halban, Schröder), develops at puberty, responds to the corpus luteum of menstruation and of pregnancy, and normally atrophies at the menopause.

(2) *Ovary.*—As regards the ovary, the analogy immediately weakens for it is only with certain accessory and perhaps abnormal ovarian structures that comparison with breast tissue may be made, since the specific ovarian cells must be considered the primary seat of the stimuli affecting the system of secondary tissues now under consideration. The structure of the ovary that has been most definitely proved to be largely controlled in its physiologic activity by the sexual cycle is the heterotopic endometrial tissue, the so-called endometrial implant (Sampson) which is known to follow closely the endometrium in many of its reactions (Robinson).

(3) *Thyroid.*—The close relation of the thyroid to the sexual function is shown by the clinical and histologic evidence of hypertrophy of the organ occurring simultaneously with similar activity in the breast and uterus. Thus there is enlargement of the thyroid at birth (Gloor), more marked, of course, in goitrous districts (von Gierke). There is increase in its size before the first menstrual period (Gundobin), which led Heidenreich to refer to a "struma antemenstrualis." There is almost certainly slight enlargement of the thyroid in many women before menstruation (Weidenmann), and in animals histologic changes have been reported in relation to the estrus cycle (Engelhorn). For many years, thyroid hypertrophy during pregnancy has been well recognized (Freund, Lange), and there is now a considerable literature on the subject in this country (Ward, Thompson, Yoakam). Certain histologic changes in pregnancy are also reported (Bell, Engelhorn). The effect of the menopause on the thyroid has been variously estimated, some authors claim an increase in activity (Schönlein, Heidenreich), others considering that the response to the menopause is variable in different women (Curschmann, Wiesel), a form of behavior having its counterpart in the irregular reaction of different breasts to the disappearance of the ovarian secretion.

It may, of course, be objected that the cause of hyperplasia of the thyroid is related to lack of iodine, but such a deficiency may be due either to a low intake or to an excessive requirement by the body, and it is on account of a relative deficiency of the latter type that hypertrophy occurs during certain periods of sexual activity (Marine).

(4) *The Prostate.*—The opportunities for cyclical fluctuations in the prostate are fewer than for the other organs, but there is development at puberty and normally atrophy in old age (Simmonds, Tenenbaum).

(*B*) There are certain mutual similarities of structure to be noted in the organs under discussion.

The parenchyma of the breast, the endometrium and the endometrial islands in the ovary, each consists of branched tubular or alveolar glands lying within a special type of loose cellular stroma, and each has the ability strikingly and rapidly to change its morphology under the influence of changes in the ovary. The prostatic glands are not dissimilar, and though having no specific periacinar stroma, its glands are also found buried in a fibromuscular supporting tissue. The histology of the thyroid alone is essentially different, but at least in comparative anatomy there is evidence of a relation to the genital organs for Gaskell has suggested that the thyroid is derived from the uterus of the palaeostracans, prehistoric forms, from which he traces the origin of the vertebrates.

(*C*) In each organ a similar series of tumors are recognized which possess a mutual similarity in constitution and structure.

(1) *Localized Benign Tumors.*—There are, of course, certain obvious differences in the structure of the circumscribed tumors as they appear in the different organs but these differences are readily laid to the variations in the structure of the tissue from which they arise and in each case the type of deviation from the normal is the same. Two of the principal differences may be explained as follows:

(*a*) The character of the stroma and its quantitative relation to the amount of epithelium in the tumors is approximately the same as in the normal organs. Thus in the thyroid there are adenomas, in the uterus adenomyomas and in the breast as a rule fibro-adenomas.

(*b*) The type of cyst which so often dominates the gross appearance of these tumors is perhaps dependent on the mechanism of disposal of the secretory products. Thus, in the endometrium with a simple duct system, the cysts are small; in the breast they may be larger, and in the ovary without ducts, the cysts may become immense.

(2) *Diffuse Hyperplasias.*—The diffuse hyperplasias exhibit a more confusing structure often combining with the essential proliferative process evidences of involution and even of chronic inflammation. Here, too, the fundamental similarity of the process as it appears in different organs becomes more evident if due allowance is made for certain structural differences in the original tissues that must be carried over to the neoplasms and for secondary variations due to differences in function and functional arrangement.

Within the group of related hyperplasias must be included: the so-called "chronic cystic mastitis"; endometrial hyperplasia; certain multicystic processes in the ovary and possibly endometriosis; colloid goiters with secondary hyperplasia and benign prostatic hypertrophy. An essential similarity between individual members of this group has been noted by many writers:

Bloodgood (1906) considered the possibility of "senile parenchymatous hypertrophy" of breast and of the prostate as of possibly the same origin as toxic thyroiditis.

Theile (1908) found a relation between chronic cystic mastitis, prostatic hypertrophy, small cystic degeneration of the ovary and goiter.

Cuttat (1912) considered prostatic hypertrophy a true fibro-epithelial degeneration having its analogy in certain fibro-epithelial tumors of breast and thyroid. Niemeyer (1921) also pointed out the resemblance between prostatic hypertrophy and the so-called mastitis chronica cystica.

Oertel (1926) has published a histologic study illustrating the similarity of the involutional and proliferative changes occurring in the breast at the menopause and in the aging prostate. He also pointed out that such changes were formerly regarded as inflammatory and hence the old names "chronic mastitis," "prostatitis" and "chronic endometritis."

Pulvermacher (1918), in the same breath, uses the terms "mastitis climacterica" and "strumitis climacterica."

Aschoff summed up this point of view by writing that "mastopathia cystica" (chronic mastitis) is a dysplastic process similar to the adenomyosis of the uterus, the adenomyosis of the prostrate, the adenofibrosis of the thyroid, all of which processes particularly affect the concerned organs in the beginning of the involutional period.

In diffuse hyperplasias as they affect the organs in question, there are four processes of which only one is of cardinal importance.

(*a*) The Formation of Multiple Cysts: There has been considerable written to favor the view that the small cysts are to be regarded as incompletely involuted remnants and often witnesses to an antecedent phase of activity. McFarland's theory that cystic disease of the breast is the result of incomplete involution of lactation acini has been touched on. Marine has shown that the colloid acinus in the thyroid is one that has been hyperplastic and has not been able to return to its original form. The multicystic ovary is regarded as a subnormal organ, the term often used being "cystic degeneration." Cystic changes in the endometrium are usually associated with hyperplasia and occur just before the menopause. The ectasia of the alveoli which Billroth regarded as the chief epithelial change in prostatic hypertrophy tends to occur in the male involutional period.

(*b*) Round Cell Infiltrations: The presence of round cells have in the past been taken as strong evidences of an inflammatory origin of the various processes in question, but there is probably much better reason to regard them as mere secondary phenomena, as part of the semiphysiologic mechanism of resorption of secretion in breast and prostate, as a result of necrosis of excessively hyperplastic tissue as in the endometrium (Schröder) or possibly simply as an accompaniment of rapid tissue proliferation.

(*c*) Increase in Connective Tissue: The increase in connective tissue is probably in part due to the age replacement of parenchymatous by fibrous tissue, but in other instances it must be regarded as an integral part of the hyperplasia and developing in a certain organic relation with the epithelium as is the case in the circumscribed tumors.

(*d*) Epithelial Hyperplasia: Epithelial hyperplasia remains the essential feature of these conditions, is responsible for their other morphologic features, for their clinical importance and is the process for which the cause must be examined.

(3) *Carcinoma.*—Certain pathologic features of the carcinomas of these organs point to a further biologic similarity within the group.

(*a*) There is a close anatomic relation to the benign forms.

(*1*) The histologic structure of the benign forms passes almost imperceptibly into the malignant.

(*2*) Areas of malignant growth are frequently found arising from or associated with benign tumors or hyperplasias. Such associations of cancer with benign forms have been reported as follows: with chronic mastitis, Tietze, Oertel, Goens, MacCarty, etc.; with fibro-adenoma, Speese; with endometrial hyperplasia, Meyer, Schröder, Fluhmann and Stephenson; with adenomyoma uteri, Cullen; with papillary cystadenoma of the ovary, Taylor; adenoma of the thyroid, Graham, Crane; prostatic hypertrophy, Tietze, Oertel, Neller and Neuburger.

(*b*) Many of the carcinomas of these five organs are intraductal or intracystic papillary tumors in their early stages, and what is especially characteristic is that their origin is frequently multicentric. For cancer of the breast, a multicentric origin has been affirmed by Askanazy, Tietze, Pribram and Lukowsky. For the bilateral papillary cystadenocarcinomas of the ovary, multiple points of development appear almost obvious. For the endometrium, Lahm wrote that he regarded a more or less diffuse origin as characteristic due to the fact that this tissue acts as a unit even in response to the stimuli producing malignant changes. Multiple cancer foci have been described in the thyroid by Langhans and noted in the prostate by Ewing.

(*c*) A final small but interesting similarity is seen in the special tendency to metastasize in the lungs and bones manifested by cancers of the breast, thyroid and prostate.

THE SUPPOSED CAUSES OF ORIGIN OF THESE TUMORS OF ALLIED ORGANS

An attempt has been made to show that the tumors of the breast are closely related to a large group of neoplasms that develop in the glandular organs related to the reproductory function. It will now be pointed out that the history of the views on the origin of many of these neoplasms has shown a gradual shift away from inflammatory conceptions toward theories based on internal causes, and in some instances specifically on abnormalities of the ovarian function.

(*A*) *Uterus.*—(1) Endometrial Hyperplasia: The endometrium presents, of course, the most perfect physiologic parallel with the parenchyma of the breast. As is still the case in the breast, the hyperplastic disease of the endometrium was disguised for many years as an inflammation under the title of "chronic endometritis" (Ruge, Scanzoni, Olshausen), and except for an isolated work of Brennecke in 1882, remained as such until Schröder and later Mayer related pathologic hyperplasia to anomalies in ovulation. As with chronic mastitis, hyperplasia of the endometrium may occur at any time during the sexually mature period of life but is most common shortly before the menopause (Schröder, Babes, Novak and Martzloff) and is rare after the climax. A peculiar type of endometrial hyperplasia is that developing late in life in association with ovarian tumors (Isbruch, Neumann, Meyer). In one such case Schröder observed carcinoma in the endometrium.

(2) Adenomyosis Interna: The diffuse penetration of the inner muscular layers by endometrial glands was also at first regarded as an inflammation on account of the teaching of Robert Meyer who used the term "adenomyositis." Frankl later showed there was no real evidence of inflammation and used the noncommittal term "adenomyosis." More recently, Meyer has changed his view and now believes that adenomyosis interna is the result of a hyperregeneration of the basal layer of the mucosa due to the too frequent demands made on the endometrium by menstruation in the latter part of sex life. Adler and Lahm have expressed somewhat similar views.

(3) Localized Uterine Tumors: The adenomyoma, the tumor most comparable with the fibro-adenoma of the breast, has been studied chiefly with regard to the ultimate origin of its cells and with little consideration for the causes of its development as a tumor. As the type of localized uterine tumor, it appears better to discuss briefly the fibromyoma, particularly since the frequent finding of glandular islands in the midst of apparently purely muscular tumors (MacCarty and Blackmann) makes it appear that a close relation must exist between these new growths and the adenomyomas (Freund, Orloff).

That the ovary, particularly an abnormally functioning ovary, is partly responsible for the growth of uterine fibroids was suggested by Seitz, in 1911. Part of the evidence that has at various times been cited in support of such a theory is as follows: the presence of a high percentage of ovaries with pathologic changes in association with myomas (Seitz); the high incidence of myomas just before the menopause; the special predisposition of women with dysmenorrhea or sterility to develop fibroids (Mayer); the special occurrence of this form of tumor in malformed or hypoplastic genitalia (Freund); the alleged hereditary factor (Aschner, lit.); the supposed existence of a special constitutional type (Freund, Aschner); the diminution in the size of myomas after the menopause or castration.

(4) Carcinoma of the Endometrium: In spite of the similarity of structure between endometrial hyperplasia and adenoma malignum, there has been considerable hesitancy in claiming an endocrine dysfunction as a factor in the production of corpus carcinoma. One author (Lahm) at least wrote that he found the origin of corpus carcinoma in the enormous capacity of the uterine mucosa for transformation on the one hand, and on the conditioning of this transformation by the ovarian hormone on the other. This view receives a little support from the frequent history of sterility and the common association of fibroids in cases of corpus carcinoma.

(*B*) *The Ovary.*—In his original paper on extra-uterine endometrial growth, Lauche regarded the serosal endothelium as the parent tissue and ascribed its metaplasia to the ovarian function, chiefly because the disease occurred exclusively in the years of sexual maturity. This age incidence can also be accounted for by Sampson's theory of transtubal implantation, but it appears that even with this conception an ovarian secretion is in a sense necessary, for it is known that an endometriosis tends to regress after castration.

If the heterotopic endometrium is actually the result of a metaplasia of the serous epithelium (Meyer, Robinson) and not an implant, it becomes the simplest member of a series of neoplasms derived from the germinal epithelium and falls into a similar genetic group with various cystic tumors of the ovary. That many serous papillary cystadenomas and cystadenocarcinomas are associated with signs of ovarian dysfunction has been pointed out in a previous paper.

(*C*) *Thyroid.*—The endemic occurrence of goiter is somewhat reconciled with the facts of enlargement of the thyroid due to glandular dysfunction by Aschoff's conception that the thyroid in goiter regions is so sensitized that it responds excessively and permanently to the normal physiologic stimuli.

That hypertrophy of the thyroid and certain nodular goiters may be associated with an ovarian disturbance is indicated by the following points:

(1) The predilection of thyroid disease for women.

(2) The tendency of goiters to develop at periods of irregular ovarian stimulation, at birth, at puberty, during pregnancy and at the menopause.

(3) The association with toxic goiters of menstrual irregularities or amenorrhea under which circumstances it has been suggested by some of the older writers (Pinard, Trousseau) that it is the ovarian disturbance which is the primary.

(4) Thyroid hypertrophy may be associated with definite pelvic disease, a point especially emphasized in this country in the writings of Hertzler. Such associated genital conditions have been myomas (Thompson, Freund, etc.); tuberculous peritonitis (Goodall and Conn); excessive sexual indulgence (Goodall and Conn, Freund).

(*D*) *The Prostate.*—The theories in regard to benign prostatic hypertrophy have followed a course similar to that of chronic mastitis. Many authors have been satisfied to debate the nature of the process, and it has accordingly been variously termed a neoplasm (Virchow, Gardner and Simpson), a compensatory hypertrophy (Simmonds), a fibro-epithelial degeneration (Cuttat). As regards the actual cause of benign prostatic hypertrophy, Ciechanowski formerly strongly advocated an inflammatory theory, maintaining that the disease resulted from a chronic gonorrheal infection which, by producing a scar tissue that constricted the ducts, terminated finally in glandular dilatation and stasis of secretions. An entirely different theory is that of Simmonds who expressed the belief that a presenile atrophy of the prostate results in a lack of prostatic secretion, which is followed by a compensatory hypertrophy of the periurethral glands, the proliferation of which into the old prostate results in the enlargement. Variations of this theory have been expressed by MacEwan, Moullin, Niemeyer and others.

There are two other aspects of the biology of the tumors under consideration which give additional evidence for an internal causative factor.

1. There is a tendency for the benign neoplasms to regress somewhat after the sex gland has been removed. In the uterus one sees this process in the successful treatment of myomas, endometrial hyperplasia and possibly very early endometrial carcinoma by irradiation, a procedure that probably has its effect by way of the ovary. Peritoneal endometriosis and the multiple peritoneal implants from papillary cystadenoma of the ovary may disappear after double oophorectomy. Diminution in the size of an hypertrophied prostate has been reported after castration and at one time was even suggested as a therapeutic measure (MacEwan, White, Moullin, Simmonds). The effects of castration on cancer of the breast are to be discussed in detail. The

effects of castration on goiters is apparently variable and seems not always to be beneficial.

2. Evidences of an hereditary influence have been found for many of the benign hypertrophies and tumors of all of these organs and such a factor has been suggested for the malignant ones. For the uterus, one finds many reports of the occurrence of myomas in families (Mayer, Aschner, lit.). For the thyroid, the subject of hereditary backgrounds is well discussed by Brain, Siemens, Vallery-Radot and others. The latter considers the hereditary factor to be in the nature of a constitutional glandular predisposition. For the ovary dermoids alone appear to occur in families. For the prostate, Simmonds stated his belief in an hereditary predisposition to benign hypertrophy.

One gains the impression that vague as any evidence for the inheritance of tumors may be, it is rather greater for the new growths of these glandular organs associated with reproduction than for neoplasms elsewhere and, should this be the case, it would appear that the hereditary factor is linked with a special constitution of the glands connected with the reproductory apparatus.

Summary.—1. Tumors of the breast are allied to the neoplasms of several other glandular organs connected with reproduction.

2. The normal causes of the proliferation of the tissues of these organs are similar, and a comparable series of neoplasms is produced in each.

3. On account of these similarities, it is unlikely that the neoplasms of one of the organs of the group should be produced by a totally different type of stimulus from that believed to be operative in the other organs.

4. There is a growing tendency to ascribe the cause of many of the new growths of these organs allied to the breast to the anomalies of the sexual function.

THE CAUSE OF CERTAIN SEMINEOPLASTIC GROWTH PROCESSES IN THE BREAST

The ovarian function can be brought a step nearer to the problem of tumor growth in the breast by a consideration of the causes of certain abnormal processes that lie on the borderline between the physiologic and the truly neoplastic.

(*A*) *Pubertas Praecox.*—That breast growth may occur at an abnormal period of life under the influence of ovarian disease is shown by the cases of precocious breast development in association with the growth of ovarian tumors (Termeer). The relation between ovarian tumor and breast growth is apparently a direct one for the mammary

enlargement may disappear after the pelvic tumor has been removed (Harris). It is interesting to note that the so-called precocious puberty associated with suprarenal disease is rarely productive of breast changes (Neurath, Glynn, Krabbe).

(*B*) *Massive Hypertrophy.*—The enormous breast growth that occurs in this disease appears frequently to be the result of abnormal ovarian function. Greig, for example, records disorders of menstruation, especially scanty menses and amenorrhea, coincident with the onset of the hypertrophy. Plummer and Bump, in reviewing the cases of the so-called adipose type, found abnormal menstruation in five of the six known cases. Blond, likewise, in summarizing all the cases that had been reported with pathologic records, concluded that the cause of the hypertrophy lay in anomalies of the ovarian function.

The relation of massive hypertrophy to the true neoplasms is probably very close. Bloodgood brought forth the interesting point that "cystic adenoma" bears the same relation to "senile parenchymatous degeneration" (chronic mastitis) that fibro-adenoma does to diffuse virginal hypertrophy. He mentioned the development of carcinoma in a case of hypertrophy, and similar malignant changes were reported years ago by Aitken and Billroth. Aitken's case report is especially interesting from the standpoint of the present paper, for his emphasis of the fact that evidences of "uterine irritation" were present at the time of the appearance of the cancer shows that a possible relationship of tumors of the breast to pelvic disease was not unthought of in 1825.

(*C*) *Painful Breasts.*—To this category belong those breasts which become painful and swollen in the week before menstruation. The possible relation of these symptoms to an actual premenstrual glandular proliferation has been discussed. An association of this condition to pelvic disease has been noted by Miller, who found a palpable gynecologic lesion in 50 per cent of his patients with painful breast nodules. Temesvary cited two cases of the older English authors (Percy, Copland), who many years ago had connected mastodynia with uterine and ovarian disorders. It is likewise not an uncommon observation at the Roosevelt Hospital gynecologic clinic that many patients with a subsiding pelvic inflammation pass through a stage in which they suffer from menstrual irregularities and breast symptoms. For certain of these painful breast conditions corpus luteum has been recommended (Lisser), but a few patients so treated at the Memorial Hospital have shown only a questionable improvement.

(*D*) *Lactation in the Nonpuerperal Breast.*—Lactation in the nonpuerperal breast is related to the present subject from two angles:

1. Secretion from the nipple is often carelessly regarded as sufficient evidence to make a diagnosis of chronic mastitis, and hence the cause

of this secretion is also the cause of a certain number of cases clinically labeled with that diagnosis.

2. The cause of the visible secretion from the nipple is probably the same as the secretion that is detectable on section in the ducts of many diseased breasts, and which is the stagnating medium on which in older women the "stasis" theory must depend.

Milk has been found in the breasts of nonpuerperal women during certain phases of the sexual cycle and in association with many forms of pelvic disease. The following conditions may be noted: (1) in relation to the menstrual cycle (Schweitzer, Gautier, Cramer); (2) following removal of the ovaries (Allsberg, Grünbaum); (3) in the menopause (Ebeler, Litten); (4) with amenorrhea from injuries (Cohn, Vogt); (5) with ovarian disease (*a*) inflammation (Hallauer, Ebeler, Ballin), (*b*) tumors (Saenger, Polano, Schmincke); (6) with fibromyomas (Freund, Herschan, Ballin, Ebeler).

In general, it appears that in the nonpuerperal breast, secretion occurs in the presence of a diminishing function of the ovary as it does under all physiologic conditions.

(*E*) *Gynecomastia.*—Deaver and McFarland reported from their careful study of gynecomastia that the disease occurs particularly in association with imperfect development of the sexual organs, pseudohermaphroditism, with atrophy or removal of the testicle. Other reports have mentioned hypernephroma (Busch), prostatectomy (Mann), tumor of the testicle (Herzenberg, Monaschkin). A case seen at Memorial Hospital developed in a young white man about fifteen months after marriage in association with a typical exophthalmic goiter. There seems little doubt, therefore, that many cases of abnormal growth processes in the male breast are also related to disorders of the sexual function.

EXPERIMENTAL EVIDENCE ON THE NATURE OF THE CAUSE OF TUMORS OF THE BREAST

The extensive study of the etiology of the mammary tumors of some of the lower animals has yielded many important facts which cannot be disregarded in determining the course that the research in tumors of the breast in man should take.

(*A*) *The Inheritance of Cancer of the Breast in Mice.*—That strains of mice may be bred in which practically all of the females will develop cancer of the breast if they survive to a certain age has been repeatedly demonstrated by a multitude of experiments, although the exact mechanism of the inheritance may still be in dispute (Little, Slye).

(*B*) *Protection from Cancer by Oophorectomy.*—A series of experiments initiated in 1916 by Lathrop and Loeb have shown that in a

tumor-bearing strain of mice the rate of tumor incidence may be lowered and the average age of onset raised by the prevention of breeding and by castration. Loeb, in 1919, amplified these experiments, finding that there was a more or less definite relationship between the number of estrus cycles that the mouse was allowed to pass through before oophorectomy and her chances of developing cancer. Cori, in 1927, confirmed these results and noted that tumors were entirely prevented by castration under twenty-two days and the normal rate of incidence was unaffected when operation was delayed until the animals were 6 months old. Murray, in 1928, using male mice of a stock in which the females showed a high tumor incidence but in which the males were never affected was able to produce cancer of the breast in 15 of 210 animals that had been deprived of their testes at the age of from 4 to 6 weeks and supplied with an ovary by transplantation from a sister. Loeb believed that the protective effects of gonadectomy were due to the removal of the corpus luteum which is responsible for the periodic stimulation of the breast tissue to growth.

(*C*) *The Development of Multiple Tumors of the Breast in Dogs.*—In support of Albrecht's conception of the organoid nature of tumor growth, Jaeger, in 1910, published a report on three cases of multiple mixed tumors of the mammae in dogs. In each case the tumors had appeared in immediate connection with "menstruation" and two of the animals, although recently mated, had failed to conceive. Jaeger considered these coincidences so unusual as to point to the conclusion that the origin of the tumors must be referred to a disturbed activity of the reproductory organs.

(*D*) *Studies in Relation to the Functional Activity of the Breast in Mice.*—Starting with a strain of mice carefully inbred, with a well known low rate of tumor incidence, Bagg has increased the incidence by subjecting the breasts to various abnormalities of lactation, such as rapid repetition of pregnancies without suckling. Such results could apparently with equal justification be ascribed to the effects of the too rapid repetition of pregnancy hyperplasia or to the irritation arising from the congestion and stasis resulting from the failure to nurse.

Bagg was also able to induce the development of cancer in the breasts of a certain number of lactating mice by ligation of the nipple. This appearance of cancer following obstruction to the flow of milk is certainly in favor of a "stasis theory," but the implications from the experiment can have only a limited applicability to the problem of tumors of the human breast so few of which originate in immediate connection with lactation.

(*E*) *The Production of Tar Cancers in Rabbit Breasts.*—Cheatle has made a point of the similarity between the reactions of the skin to

the application of tar and the series of epithelial hyperplasias which he has described as occurring in the breast. He cited this as support for his belief that these breast conditions are also the result of a local irritant. In view of this argument, it is interesting to note that the injection of various tar preparations into rabbit breasts by Yamagiwa and Murayama resulted only in the production of a certain number of cases of "cancroid and adenocancroid." The authors themselves write: "We found that the secreting glandular epithelia do not respond to the irritation of tar but soon perish. For this reason we were unable to produce true glandular carcinoma."

It may be a fact of very great significance that tumors in mice with their strong hereditary influence and their characteristic of being affected in their incidence by oophorectomy are glandular cancers as in women, whereas attempts to produce cancer in breasts of rabbits by a local irritant result only in epitheliomas!

(*F*) *The Effect of Castration on Carcinoma of the Breast in Women.*—Near the beginning of the present century, oophorectomy for inoperable cancer of the breast attained a short vogue. The rationale of this treatment was logically arrived at by Dr. G. T. Beatson, who had observed a certain resemblance between the mammary changes in pregnancy and those of early cancer and hoped accordingly that castration might produce a fatty degeneration in the cancer cells. Beatson's first few cases in which this method of treatment was used were reported in 1896 and gave evidence of at least a temporary beneficial effect from the operation.

Following Beatson's original article, the operation was repeatedly attempted and about a hundred cases were reported in England by Hermann, Boyd, Thompson and Lett, a few cases in Germany by Cahen and a few in America by Robert Abbe. The reports of many of the writers mentioned emphasized that oophorectomy produced the best results when performed on women developing cancer before the menopause and also that the greatest diminutions in size following the treatment were to be expected in the relatively slow growing tumors producing local recurrence without metastasis. Since such behavior is that of the more differentiated histologic forms of cancer of the breast, the response described is quite analogous to the regression of the semimalignant implants on the peritoneum following bilateral oophorectomy for papillary cystadenoma of the ovary.

PREVIOUS VIEWS ON THE ORIGIN OF TUMORS OF THE BREAST

The general classification of the epithelial neoplasms of the breast into the fibro-adenoma, "chronic mastitis" and carcinoma offers three types of neoplastic processes for study. A word must be said about the previous ideas on the nature and origin of these special forms.

(*A*) *Localized Benign Tumors.*—Most authors agree that all the benign, solid encapsulated tumors of epithelial and connective tissue, in whatever proportion, belong genetically to a single group. Certain writers (Cheatle, Charlatow) appear to separate the so-called "pure adenoma" slightly. Wilms regarded all these growths as mixed tumors in the strict sense, namely, that they are derived from anlagen segregated from both germinal layers. Ribbert also classed these tumors as fibro-epithelial but not actually "mixed," for he implied only that epithelium and connective tissue were growing in mutual interdependence. Albrecht classed the fibro-adenoma as a "hemartome," a form due to a defective mixture of the constituent tissues but closely allied to the normal organ.

Another point of view was taken by Beneke who was greatly influenced by the then popular doctrines of Roux on the dominating rôle played by the epithelium in the determination of tissue form (see also the recent discussion by Fischel). After studying the parallelism between fetal breast development and the formation of benign tumors, Beneke concluded that the epithelium was the primary and guiding factor in both instances, and for him all fibro-epithelial tumors were essentially adenomas. Other authors prefer to place the emphasis on the connective tissue component. In a recent article on benign tumors of the breast, McFarland recommended the term suggested by Warren, namely, periductal fibroma, for the common type of localized benign tumor. Cheatle, though not permitting himself much theorizing, appears from his minute descriptions of the histologic effects of hyperplasia "intra-elastica," "extra-elastica" and "elastica" to place a high degree of importance on the connective tissue changes.

In the consideration of the localized tumors, it appears obvious that one must consider two processes: (1) the cause of the segregation of the special group of cells which give rise to the tumor and (2) the reason for the development of these germs. Whether the germs of the mammary tumors become differentiated from the rest of the tissue during fetal life or later, must remain a theoretical consideration. Since the puberty period of the breast corresponds with the fetal stage of many of the body organs, it would not be inconsistent with the theory of embryonal segregation of tumor germs to suggest that possibly the differentiation of certain growth foci takes place at that time. The cause of the further growth of fibro-adenomas is certainly in part connected with the sexual function, for such tumors make their appearance as a rule soon after puberty and are extremely unusual in childhood, after the menopause or in the male breast. More direct evidence for a special ovarian dysfunction as productive of fibro-adenomas is cited under the discussion of the endocrine origin of "chronic mastitis" since most authors have discussed the two conditions together.

(*B*) *Diffuse Hyperplasia—"Chronic Mastitis."*—The cause and nature of this disease have been a popular subject for scientific debate for at least thirty years. The early studies of Cooper, Brodie, Velpeau and Reclus were chiefly independent and excited little antagonism, but, in 1892, Schimmelbusch published a work calling the disease a "cystadenoma," and in the following year Koenig proposed the title "mastitis chronica cystica." Thus the lines were drawn between two distinct theories, inflammatory and neoplastic. In the next few years, both views received support and attempts at modification from many writers. For the inflammatory theory may be mentioned Roloff, Lichtenhahn, Maly and Delbet; for the neoplastic, von Saar, Brissaud, Cornil and Keibel. Certain authors such as Sasse and Curtis and Wood found evidence of both processes being active.

As it gradually became obvious that the disease could not be categorically classified, new attempts were made to define microscopically the nature of the changes. As a result, some authors have emphasized particularly the epithelial proliferation, among which have been Berka, Tietze, and more recently, Cheatle. Other writers have considered as primary the connective tissue changes, this being the view supported by Greenough and Hartwell, Dietrich, Todyo, Berthels, Lexer and Lukowsky. With the former, the disease became an epithelial hyperplasia closely approaching true tumor growth, with the latter a fibromatosis often connected with the general presenile changes.

The chief views on the etiology of chronic mastitis that appear still to have a claim to consideration are as follows:

(1) Theory of Malformation: This theory rests chiefly on the studies of Krompecher who came to the conclusion that the cysts of acidophilic cells in the breast were similar to the sweat gland cysts of the axilla, and as he regarded such cysts as the most characteristic feature of "chronic mastitis," he decided that this disease represented an atavistic malformation in the direction of sweat gland form. Krompecher's theory has received very little confirmation by other writers and has been contradicted by Askanazy, Lukowsky and others.

(2) Theory of the Stasis of Breast Secretion: This theory is the modern version of the older inflammatory view of origin of chronic mastitis. The theory takes two forms, dependent on the theoretical source of the stagnating substance:

(*a*) Stasis of the secretions of lactating breast due to faulty nursing. Adair and Bagg have emphasized this as a factor in the cause of cancer in their study of the nursing histories of 200 women with carcinoma and have also demonstrated the effect of stasis by the already cited experiment of the ligation of the nipple in mice. Keynes believed that the earlier incidence of chronic mastitis in single women was due to the lack of proper drainage usually afforded by a pregnancy.

(*b*) The stasis of the secretion of the nonlactating breast. Keynes based his case on the fact that there was always some secretion in the milk ducts and on his demonstration of the complete obstruction to the outflow of this material through the presence of a plug of desquamated epithelium that under ordinary circumstances completely closes the orifices in the nipple. According to Keynes, the cause of the epithelial changes in "chronic mastitis" lies in the chemical irritation of the stagnated secretion. To prove that such material may incite proliferation, he cited A. H. Drew, who had shown that cellular growth was stimulated by the products of autolysis. Keynes believed that there was no relation between this breast disease and involutional changes, but two of his predecessors in the stasis theory, Berthels and Lukowsky, placed the primary change in the connective tissue, which by its constriction of the ducts prevented proper drainage.

The stasis theory depends much on the histologic evidence supplied by the presence of the round cell infiltrations to show that a chronic irritation exists. The semiphysiologic significance of these round cells has been previously touched on.

(3) Involution Theory: Involution cysts were mentioned by Billroth, in 1880, but the idea that the whole process was connected with involution has been slow to develop and has taken many different forms. In 1905, Warren designated the condition usually called chronic mastitis "abnormal involution," but the name did not become popular. Paul Thiele considered the disease a somewhat different process which he termed "fibro-epithelial degeneration." Aschoff called it a dysplastic condition. Lukowsky and Berthels, Lexer and Dietrich considered that the primary fibrosis of the breast may have an involutional significance. The idea of an abnormal involution following lactation is also suggested by McFarland in his treatise on residual lactation acini.

The most specific of the views of this group was advanced by Bloodgood, who called the disease "senile parenchymatous hypertrophy," thereby emphasizing that the essential process or at least that with the greatest potentiality was the increased activity of the glandular elements. It is the histologic conception which most closely coincides with the studies of the present paper. Bloodgood even suggested that the intoxicant productive of subjective symptoms in the menopause might be operative in producing the structural changes in the breast.

It is obvious from this discussion that an involutional element in the production of "chronic mastitis" is not incompatible with the truth of either the stasis or hormonal theory.

(4) Endocrine Theory: That Bloodgood believed that the menopausal intoxication might have an effect on the breast has already been noted. In 1919, Pribram, in a purely theoretical article, suggested that

during the involutional process, after many cells had become senile, a few remaining youthful ones still capable of response would proliferate unimpaired under ovarian excitation. Bartlett and Miller have in this country made certain clinical observations on the occurrence of benign hypertrophies of the breast in association with pelvic pathologic processes. Dietrich and Kueckens also have written in favor of the view that abnormal proliferation of the breast tissue is related to irregular ovarian activity, particularly during the involutional period.

The chief proponent of the ovarian theory of origin of abnormal hypertrophies of the breast has, however, been Moszkowicz, whose studies and those of his predecessors on the histology of the menstrual cycle in the breast have already been discussed. From this point Moszkowicz turned to the consideration of the less circumscribed breast lumps that are tender at menstruation. The histology of these lumps was found to be a hyperplasia of the gland fields, an excessive response to the premenstrual stimulation. Transitional forms were then noted between these hyperplasias and the fully developed fibro-adenoma which caused Moszkowicz to assign to the latter a similar origin (fig. 3). According to the same author, the changes observable in glands with "chronic mastitis" consist in an untimely hyperplasia of all the elements caused by an ovarian dysfunction and quite analogous to the hyperplastic changes in the endometrium. Moszkowicz considered carcinoma to be the result of the same type of stimulation, chiefly, apparently, because of the association of this disease with the benign conditions (fig. 4). The ultimate causes of tumor growth that affect the breast through the sexual organs are probably varied and may include such conditions as constitutional inferiority of the sex glands, toxic injury to the sex glands, endocrine disease and sexual irregularities. Moszkowicz cites little proof of his theories, does not analyze his clinical material to any extent, seems unduly mechanistic in the finer details of his theory and entirely hypothetic in his list of underlying causes. Yet the theoretical possibilities of abnormal growth in the breast in response to ovarian stimuli, as he has suggested it, and particularly with regard to the close parallel with conditions as found in the endometrium, appear quite sound.

(*C*) *Carcinoma.*—The theories of the cause of cancer in the breast have followed closely those for the benign conditions, especially those for the diffuse process, because few observers of "chronic mastitis" have failed to find evidence of associated carcinoma and so have provisionally extended their theory to include the malignant forms. Hence the theories of the origin of cancer may be for convenience divided in the same manner.

(1) Carcinoma derived from sweat gland cells, the result of malformation. This view again is chiefly supported by Krompecher.

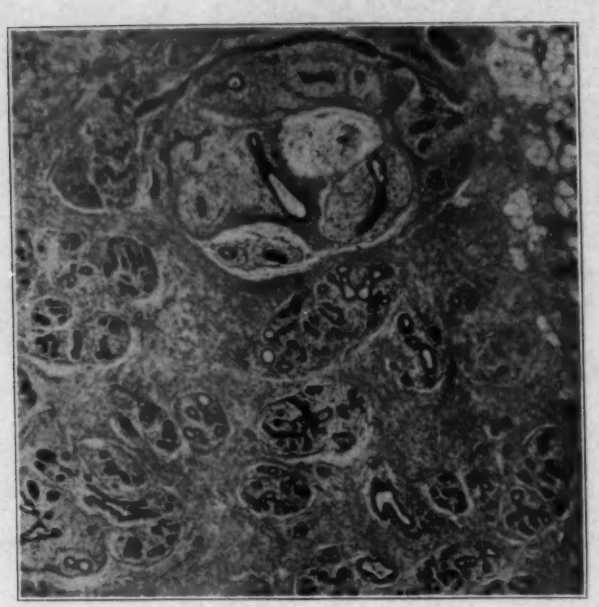

Fig. 3.—Transition from glandular hyperplasia to fibro-adenoma. (After Moszkowicz: Arch. f. klin. Chir., Berlin [Julius Springer] **144**:138, 1927.)

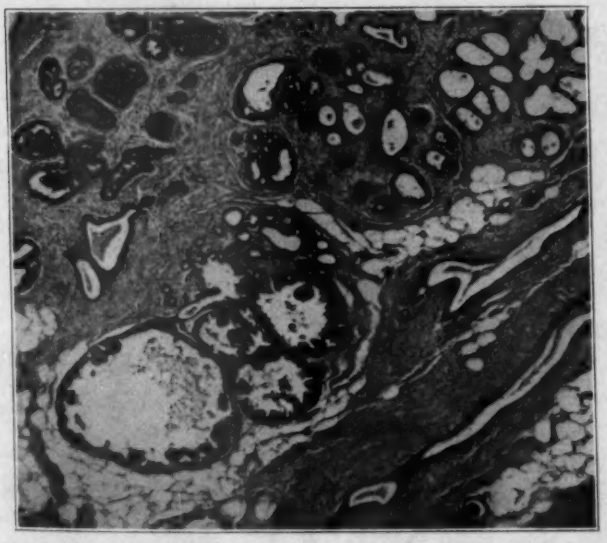

Fig. 4.—Cystadenoma and fibro-adenoma with cysts filled by proliferating epithelium and exhibiting an early stage of malignant transformation. (After Moszkowicz: Arch. f. klin. Chir., Berlin [Julius Springer] **144**:138, 1927.)

(2) Carcinoma as the result of irritants from stasis of secretion. As supporters of this view are once more Adair and Bagg, Keynes, Berthels and Lukowsky.

(3) Carcinoma incidental to certain involutional changes. This point of view has recently been discussed by Oertel in connection with presenile changes in both breast and prostate.

(4) Carcinoma from ovarian dysfunction. The early views of Beatson on the subject, the evidence from animal experimentation, the theoretical concepts of Pribram and Moszkowicz have been discussed.

The attack on the problem of cancer of the human breast has been from two different points.

(1) The Histologic: Here the case rests on the evidence of a multitude of authors who have described the pathologic association of cancer and chronic mastitis and the fineness of the histologic boundary between the two (see Tietze, Berthels, Lukowsky, MacCarty, Reclus, Schimmelbusch, Keynes, Ewing, Oertel, Fischer and others). The association in all probability indicates either that the carcinoma is the derivative of the chronic mastitis or that the two are varying expressions of a similar process with a related cause.

(2) The Statistical: The static picture afforded by microscopic preparations can scarcely be hoped to afford proof of the nature of the relations of the benign to the malignant growths. Attempts at production of cancer in man under predetermined conditions are not possible. The ultimate understanding of the origin of cancer must therefore result from a study beginning with the patient with cancer and attempting to sort out from the multitude of innocuous stimuli which her breast has received, the specific ones, if there are such, that produced the cancer.

What seems to be the most careful etiologic study yet executed in a series of cases of cancer of the breast was published in 1926 by Dr. Janet Lane-Claypon. This work was based on the histories of 508 cases of cancer and 509 noncancerous controls obtained by a group of eight observers in several English and Scottish hospitals. The opportunity thus afforded for collectively obtaining a large amount of accurate material produced a report that must claim precedence over most if not all previous work and which is distinctly discouraging to individual effort.

The most important result of Dr. Lane-Claypon's studies appears to be the definite proof of higher relative incidence in nulliparous women. From this fact and from a short discussion of histology, the author draws the cautious conclusion that the continually recurring changes of the menstrual cycle—whatever their precise nature—have an important bearing on the whole process of hyperplasia and carcinoma. At least

she says that her statistics point decidedly against the belief that cancer is more liable to occur in women whose breasts have been used for suckling at repeated pregnancies or in those who have been subject to abscess or suppuration in the course of lactation.

The following study cannot be compared with the just discussed report for magnitude or for detailed statistical analysis. It is hoped, however, that a little may be accomplished by approaching the problem from a considerably different angle, particularly by more completely individualizing the cases so that the development of cancer can be studied in relation to the state of the breast at the time of the appearance of the tumor rather than in relation to antecedent behavior or injuries.

(To be Concluded)

OSTEOGENIC SARCOMA OF THE HUMERUS

REVIEW OF THE LITERATURE AND CASE REPORT*

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A case of telangiectatic sarcoma of the humerus seen recently at the University of Virginia Hospital presents several features that seem sufficiently interesting to warrant a report. It has been submitted to the Registry of Bone Sarcoma for study. Because the case illustrates certain aspects of the disease mentioned by Ewing, Kolodny and others, a brief summary of the recent literature dealing with osteogenic sarcoma will be made.

REPORT OF CASE

History.—R. M., a mulatto boy, aged 17, was admitted to the University of Virginia Hospital on Jan. 14, 1929. The family and past history was entirely negative. The chief complaint was enlargement of the left shoulder of one week's duration. Because of slight soreness, which had increased gradually, his attention had been attracted to the shoulder about three weeks prior to the time of his admission. Motion in the joint had been slightly limited because of pain. No enlargement or other change in the appearance of the part had been noticed, however, until the end of the second week. At that time swelling became apparent, and subsequently the shoulder increased in size rather rapidly.

There had been no fever, chills, sweats or other systemic complaints or symptoms. No history of any injury or trauma to the shoulder was elicited.

Examination.—Examination revealed a well nourished and fully developed colored boy (fig. 1). The temperature was 101 F., the pulse rate 100 and respirations 20. The systolic blood pressure was 128 and the diastolic 80. Physically, he seemed entirely normal except for the left shoulder. It was moderately enlarged and had a slightly fusiform appearance because of swelling of the anterior and lateral aspects of the region, which decreased in size as it extended downward toward the anterior axillary fold (fig. 1 *B*). The skin was shiny and tense over the mass, and there was some increase in the local temperature. Palpation of the mass caused pain, and there was slight pitting with pressure. There was a definite feeling of fluctuation in the deeper structures. Motion of the arm at the shoulder was moderately limited because of the pain which attended both active and passive movement of the joint.

Examination of the urine revealed no abnormality. The hemoglobin was 85 per cent; the red cells numbered 4,580,000, and the leukocytes, 11,400. The smear and differential count were normal. The Wassermann reaction was negative, and no growth was obtained from a blood culture. Roentgenograms of the chest showed nothing abnormal. Stereoscopic roentgenograms of the left shoulder

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revealed a motheaten area of destruction of the shaft of the left humerus extending from the region of the epiphyseal line downward for a distance of about 8 cm. There were some detachment and bulging of the periosteum of that area. On the lateral aspect there was a fine, threadlike area of increased density about 2.5 cm. in length projecting outward and slightly upward from a point of attachment in the region slightly distal to the epiphyseal line (fig. 2). The roentgenologic diagnosis was: "probable osteogenic sarcoma of the left humerus." The possibility of chronic, low-grade osteomyelitis, however, could not be excluded entirely. Roentgenograms of the remainder of the skeleton showed no abnormality.

The mass was explored with an aspirating needle, and about 10 cc. of bloody, serous fluid was recovered from what appeared to be a multilocular cavity, in the walls of which there seemed to be a deposition of calcareous material. Smears and cultures of the fluid failed to reveal either organisms or tumor cells. A guinea-pig, into which injections of some of the material were made, showed no evidence of tuberculosis after six weeks. A biopsy was made on January 21. The pathologic diagnosis made from the tissue was: "osteogenic sarcoma, telangiectatic with peritheliomatous arrangement of the cells."

Fig. 1.—Patient at the time of admission. *A*, only slight enlargement of the left shoulder. *B*, lateral aspect of the shoulder.

Treatment.—Treatment with Coley's mixed toxins was initiated on January 29. One-fourth minim (0.015 cc.) was given for the first dose, and each time the amount was increased until 3.5 minims (0.21 cc.) was reached. The first injections were given intramuscularly; subsequent doses, directly into the tumor. The average rise of the temperature following the injections was to 104 F., and the highest, to 106 F. The injections were discontinued on February 15, after fifteen injections, because of continuous elevation of the patient's temperature and his precarious physical condition.

Course.—The course of the disease was extremely rapid (fig. 3). One month after the patient's admission to the hospital the mass had tripled in size, the hemoglobin was 55 per cent and the red blood cells numbered 3,620,000 (fig. 4). Two months after his admission, the mass was more than 35 cm. in diameter, the hemoglobin was only 35 per cent and the red cells numbered 2,500,000 (fig. 5). At that time the tumor began to break down and became a fungating, necrotic mass. Handfuls of necrotic tissue sloughed from the interior of the tumor on several occasions. On March 28 and April 1, several hemorrhages occurred. On April 1, death ensued within a few hours of a severe hemorrhage.

Necropsy.—Postmortem examination revealed the necrotic tumor mass already described. There was a pathologic fracture of the surgical neck of the humerus

Fig. 2.—Roentgenogram of the left shoulder at the time of admission.

Fig. 3.—Roentgenogram of the left shoulder one month after admission.

(fig. 6). Except for a small metastatic nodule about 1 cm. in diameter in the lower part of the upper lobe of the left lung, no evidence of metastasis of the growth was found. No other positive observations were made.

REVIEW OF THE LITERATURE

Prior to 1920, when the Registry of Bone Sarcoma was organized by Codman through the American College of Surgeons, there was widespread misunderstanding in regard to the classification, pathology, clinical course, prognosis, diagnosis and treatment of tumors of the bone. In 1920 Kolodny stated that the diagnosis was erroneous in one half of all cases diagnosed as sarcoma of the bone by the clinician and pathologist.

Fig. 4.—Anterior and lateral views of the shoulder one month after admission.

Since that time certain aspects of the subject have been greatly clarified by intensive study of the material of the Registry. Notable contributions have been made by Bloodgood,[1] Christensen,[2] Codman,[3] Ewing,[4]

1. Bloodgood, J. C.: How to Diagnose and Treat a Bone Lesion, J. Bone & Joint Surg. **8**:470 and 727, 1926; **9**:217, 1927.

2. Christensen, F. C.: Bone Tumors: Analysis of 1,000 Cases with Special Reference to Location, Age and Sex, Ann. Surg. **81**:1074, 1925.

3. Codman, E. A.: The Registry of Cases of Bone Sarcoma, Surg. Gynec. Obst. **34**:335, 1922; Registry of Bone Sarcoma: I. Twenty-Five Criteria for Establishing the Diagnosis of Osteogenic Sarcoma; II. Thirteen Registered Cases of "Five-Year Cures" Analyzed According to These Criteria, Surg. Gynec. Obst. **42**:381, 1926.

4. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 1127.

Kolodny [5] and others. Kolodny's monograph is classic. It represents a comprehensive personal study of 700 cases of the Registry and an extensive review of the literature.

Incidence.—Christensen analyzed 1,000 cases of tumors of the bone assembled from the Registry and certain other sources. He studied

Fig. 5. Anterior and lateral views of the shoulder two months after admission. Note the great vascularity of the skin and the fungation of the tumor at the site of the biopsy.

the material particularly with reference to the location of the tumors and the age and sex of the patients. He found that the most frequent

5. Kolodny, A.: Bone Sarcoma: The Primary Malignant Tumors of Bone and the Giant Cell Tumor, Surg. Gynec. Obst. **44**:214 (April) 1927.

site of osteogenic tumors, both benign and malignant, was at the ends of the long bones where there is an epiphyseal disk of maximum growth, where the growth period is longest and where the growth momentum is greatest. Of osteogenic sarcomas, 58.7 per cent were in males and 41.3 per cent in females. Osteogenic sarcoma occurred oftenest in the second decade of life, reaching a maximum incidence at the age of 15 years. At no period of life, however, was there complete immunity.

Of all sarcomas one in three was osteogenic, and the knee was the most frequently involved part of the body. Fifty-two per cent of oste-

Fig. 6.—The tumor at the time of necropsy. Note the upper end of the humerus lying free in the tumor, which had become necrotic and sloughed extensively.

ogenic sarcomas occurred in the femur, 20 per cent in the tibia and 9 per cent in the humerus. The remaining 19 per cent were distributed among the other bones of the body. It is interesting that no case of osteogenic sarcoma of the lower end of either the radius or the tibia has occurred in the material of the Registry.

Etiology.—Intensive study has failed to throw much light on the etiology of osteogenic sarcomas. Kolodny mentioned the gradations of cases from those with tissue not unlike callus to those with very cellular tissues. He suggested that the development of osteogenic sarcoma is

probably guided by the same principal laws of growth that are usually observed in the animal organism when in the stage of natural growth or when repair and regeneration take place. Some unknown stimulus breaks the "growth restraint." Trauma has frequently been suggested as such a stimulus. In a recent paper, Knox [6] made a study of trauma in relation to tumor formation and concluded that a single trauma had rarely if ever been proved conclusively to be of etiologic significance.

Classification.—The term "osteogenic" (Ewing) indicates that the tumor has arisen from cells the function of which it is to form bone but which may or may not do so. When bone is actually formed, the tumor may be still further qualified as "osteogenetic." The following classification of tumors of the bone was adopted by the Registry as a basis for study:

1. Metastatic tumors primary in tissues other than bone
2. Periosteal fibrosarcoma
3. Osteogenic tumors
   (*a*) Benign
   (*b*) Malignant

I. Periosteal
II. Medullary and subperiosteal
III. Sclerosing
IV. Telangiectatic

4. Inflammatory conditions
5. Benign giant cell tumors
6. Angiomas
   (*a*) Benign
   (*b*) Malignant
7. Ewing's tumor
8. Myeloma

Kolodny discussed this classification and pointed out certain insufficiencies in it. He mentioned the importance of classification according to cell origin rather than cell type for in the same tumor different areas may show many different structures, such as fibrosarcoma, cartilage or bone. He suggested that until more accurate data were available all primary malignant bone tumors be subdivided into four groups:

1. Osteogenic sarcoma
2. Ewing's sarcoma
3. Myeloma
4. Unclassified sarcoma including angio-endothelioma and extraperiosteal sarcoma

6. Knox, L. C.: Trauma and Tumors, Arch. Path. **7**:274 (Feb.) 1929.

Pathology.—Kolodny characterized osteogenic sarcoma as a tumor derived from cells that are descendants of mesoblastic elements predestined embryologically to form bone. Hence these cells have the potential ability to differentiate into osteoblasts. In the differentiation there are many intermediate stages and therefore many different structures in the same or different tumors.

The commonest cell type in osteogenic sarcoma is the spindle cell, usually the small variety with a hyperchromatic nucleus. The epulis type of giant cell and the round cell are no longer classed among those found in sarcoma of the bone. The chief morphologic difference between osteogenic sarcoma and other malignant tumors is its intercellular substance, which may be hyaline, osteoid, cartilaginous, myxomatous or osseous.

Spontaneous lymphocytic infiltration in the absence of previous biopsy or treatment seems to indicate some defense reaction to the tumor on the part of the body. All of the Registry cases of five year cures showed this phenomenon, but not all cases that showed it were cured for five years.

Clinical Course and Prognosis.—The onset may be and frequently is insidious. In the early stages of the disease many patients have been treated for rheumatism because of pain in the region of a joint. The tumor may not become apparent for some time. The rapidity with which it grows usually depends on the degree of its malignancy. The prognosis, while apparently poor in all cases, depends on the degree of malignancy of the tumor. In 1922, one and one-half years after the Registry was instituted, Codman stated: "We know of only four cases of true osteogenic sarcoma which are alive in this country today, who were treated over five years ago. These were treated by amputation alone." In 1926, he analyzed thirteen "five-year cures" and stated that in the majority of these cases some doubt as to the certainty of the diagnosis had been expressed by some of the reviewing pathologists.

Diagnosis.—According to Ewing, persistent, increasing and unexplained pain is the most significant and the earliest symptom in nearly all cases. This is apparently due to the stretching of the sensitive periosteum by the growing tumor. It calls for the provisional diagnosis of osteogenic sarcoma at once. The general health of the patients is nearly always good. More or less fixation of the soft parts and increase in the venous circulation of the skin are observed early in most cases. Some local heat and a slight elevation of body temperature are not uncommon.

The roentgenogram is of the greatest diagnostic importance. Its chief features are roughening of the outer surface of the shaft and lifting of the periosteum at the advancing edge of the tumor, the "reactive triangle" of Codman.

Biopsy may be employed as a diagnostic aid in certain cases. Goodwin,[7] in discussing tumors of the bone, recognized three types of cases diagnostically. In one group were those in which the diagnosis of malignancy was apparent, in another those in which the evidences of benignity were certain. In between these were borderline cases in which the history, the physical observations and the roentgenograms were not conclusive, cases in which accurate differentiation between a benign and a malignant lesion was most important in order to decide between conservative and radical treatment. He stated that only in this group of cases does biopsy serve a useful purpose. In the other groups it is usually unnecessary. Furthermore, a biopsy made merely as a matter of record in inoperable cases is unfair to the patient because of the consequent stimulation to tumor growth and the subsequent fungation of the tumor which is almost certain to follow this procedure, thereby adding to the misery of the patient until he is relieved by death. When resorted to, biopsy must be done between tourniquets to prevent dissemination of malignant cells. If the tissue proves malignant, immediate amputation is indicated.

Treatment.—Ewing characterized the treatment for osteogenic sarcoma as "a difficult and complex subject calling for skill and experience." Its results are unsatisfactory. These tumors resist irradiation and become more painful and somewhat swollen before the resulting slow regression sets in. Preliminary irradiation as a therapeutic test and as a preoperative measure is thought worth while by Ewing. He stated that he was unable to evaluate the effects of Coley's[8] toxins in cases of osteogenic sarcoma. Codman expressed the belief that amputation plus Coley's toxins offers the best chance of cure.

Telangiectatic Group.—The telangiectatic variety of osteogenic sarcoma presents certain special features of interest in connection with the case reported.

As the name implies, this is a very vascular tumor. The vessels may be so large and numerous that the tumor pulsates, giving rise to the term "malignant bone aneurysm." Such tumors develop very rapidly, destroy the shaft early with resulting pathologic fractures and yield metastases with a fatal termination within a few months. The growth is usually composed of a series of communicating blood sinuses lined by hyperchromatic spindle and polyhedral cells and supported by strands of partly ossified tumor tissue. The periosteum is soon perforated, and the tumor

7. Goodwin, W. H.: Tumors of the Bone: A Comparative Study, Arch. Surg. **18**:2353 (June) 1929.

8. Coley, W. B.: The Differential Diagnosis of Sarcoma of the Long Bones, J. Bone & Joint Surg. **10**:420, 1928.

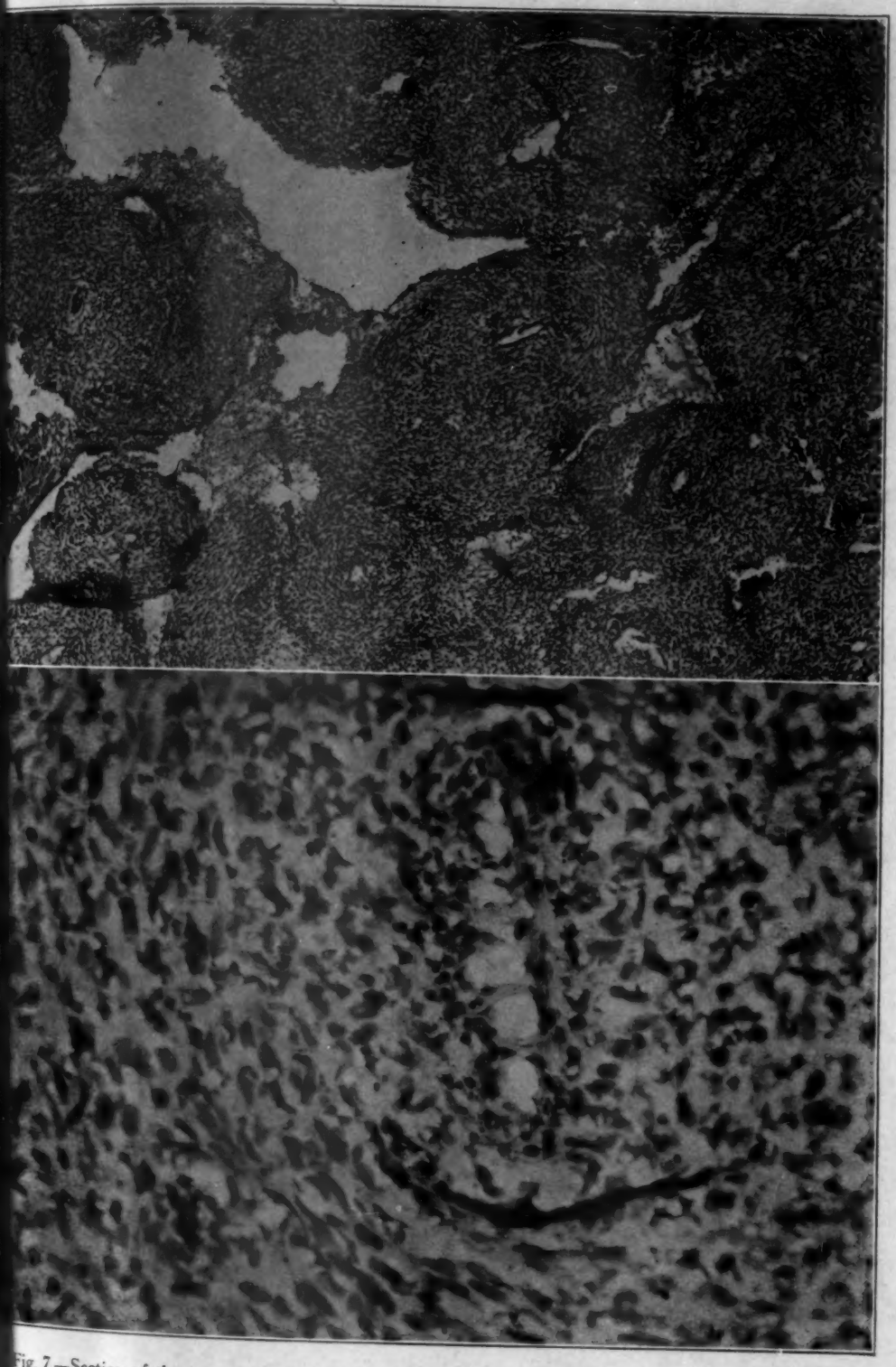

Fig. 7.—Section of the tumor (biopsy). The upper part has a magnification of 50; the lower, 300.

sinuses ramify through the muscles or into the joint. A considerable segment of the diaphysis may be found free in the center of the blood mass.

Except in the early stages, the roentgenogram fails to reveal the usual features of osteogenic sarcoma. The elevation of the periosteum is soon obscured by the complete destruction of the shaft of the bone and the periosteum. Such tumors progress very rapidly, and a serious condition is reached within a few weeks. These tumors carry the worst prognosis of any group, and Ewing said that as far as he could learn, all cases of this form of sarcoma have proved fatal.

COMMENT

The most outstanding clinical features of this case were the extreme rapidity of growth of the tumor and the immense size attained by it. Only four months elapsed between the time of the onset of the first symptoms and the death of the patient. In spite of the rapid growth and great malignancy of the tumor, however, only one metastatic tumor was found at necropsy.

The age of the patient corresponds closely to that of the maximum incidence of the disease as given by Christensen. There was no history of antecedent trauma, and no other apparent etiologic factor was discovered.

The influence of the biopsy on the course of the disease is difficult to determine with assurance. The tumor had already broken through the periosteum and invaded the muscles of the arm when the biopsy was made. It is certain, however, that the biopsy must have been directly responsible for the early fungation of the tumor. In view of the many vascular channels that must have been made accessible to detached tumor cells at the time of the biopsy, it seems remarkable that no more than one metastatic tumor was found at necropsy. The small size of this nodule suggests implantation at a much later time than that of the biopsy when the rapidity of growth of the mother tumor is considered.

The structure of the tumor illustrates the point made by Kolodny that different areas of the same tumor frequently show many different structural characteristics. In this case the tissue removed at biopsy was typically telangiectatic, while sections from other portions of the tumor taken at necropsy revealed various different structural characteristics (figs. 7, 8 and 9).

The diagnosis presented an interesting problem. The relatively acute onset; the pain, tenderness, swelling, local heat and fluctuation; the elevation of the patient's temperature and the number of leukocytes suggested the possibility of a low-grade osteomyelitis of the humerus. Even the roentgenogram showed some of the features commonly found in osteomyelitis.

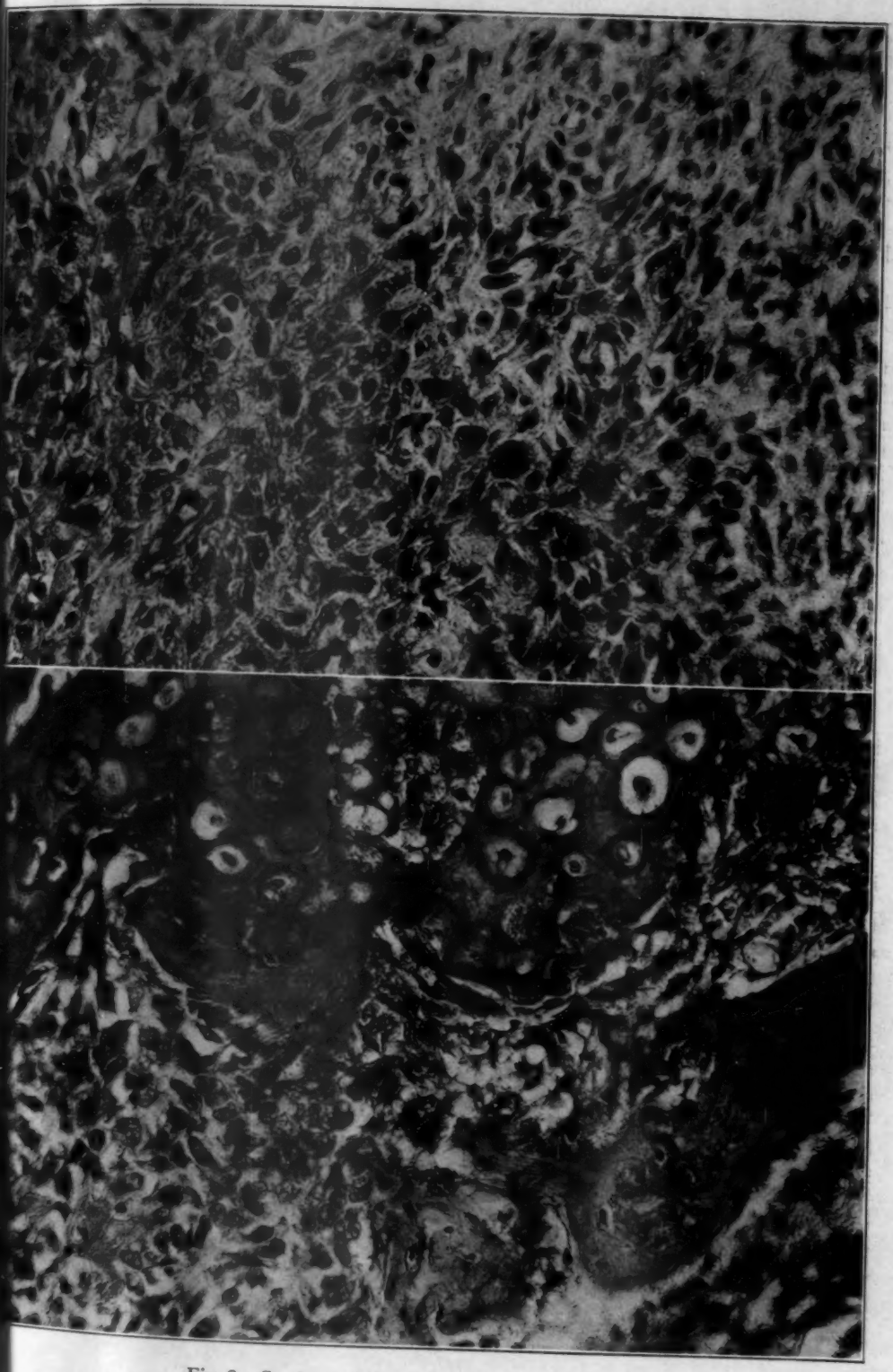

Fig. 8.—Sections of the tumor (necropsy); × 300.

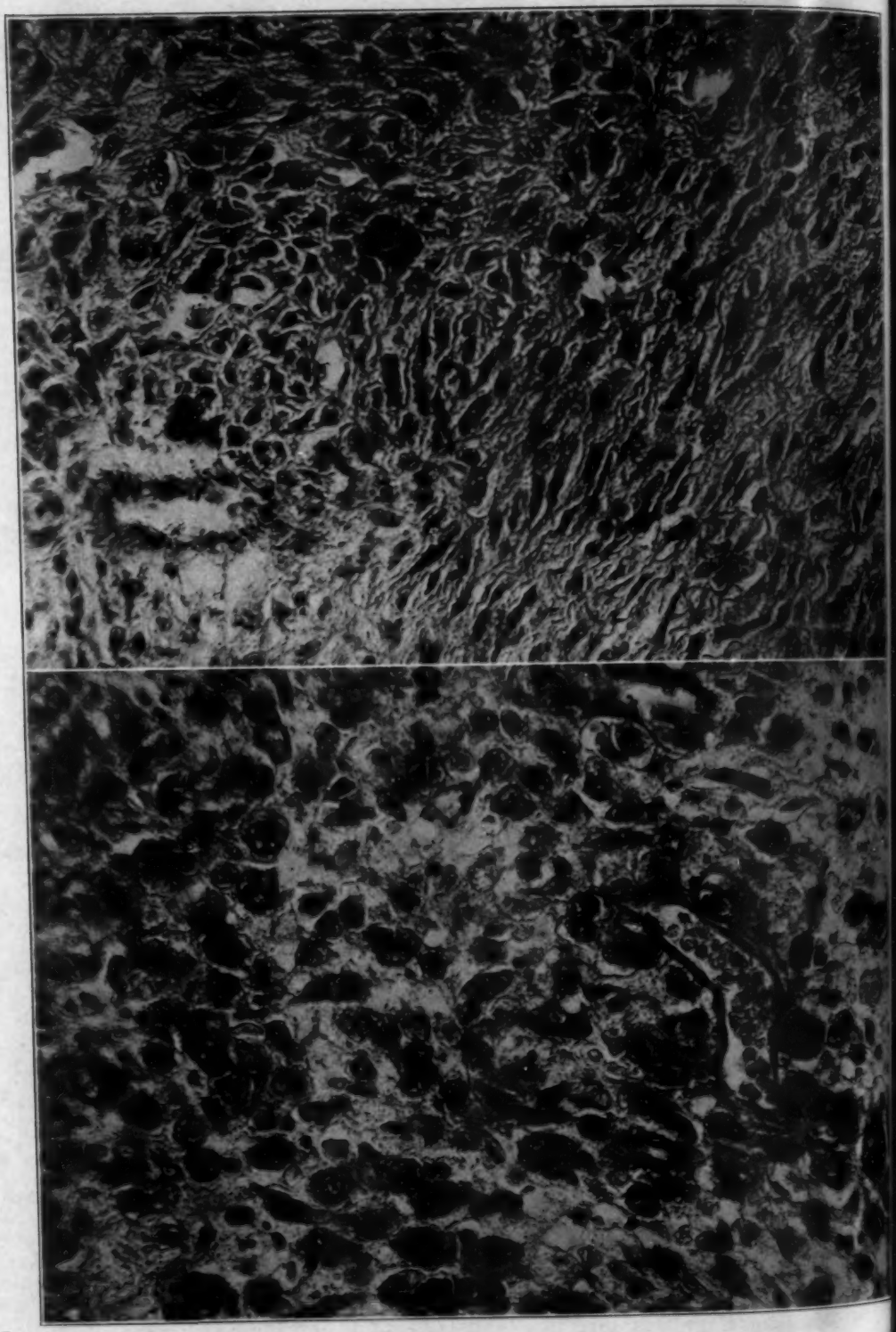

Fig. 8.—Sections of tumor (necropsy); × 300.

The course of the disease and the fact that only one small metastatic tumor was found at necropsy cause one to regret that the patient was not given the chance, poor though it might be, offered by a shoulder-girdle amputation. Such an excision of the tumor would have almost certainly prolonged the patient's life and at least saved him from the discomforts caused by the local growth. Coley's toxins did not seem to be of any value in this case.

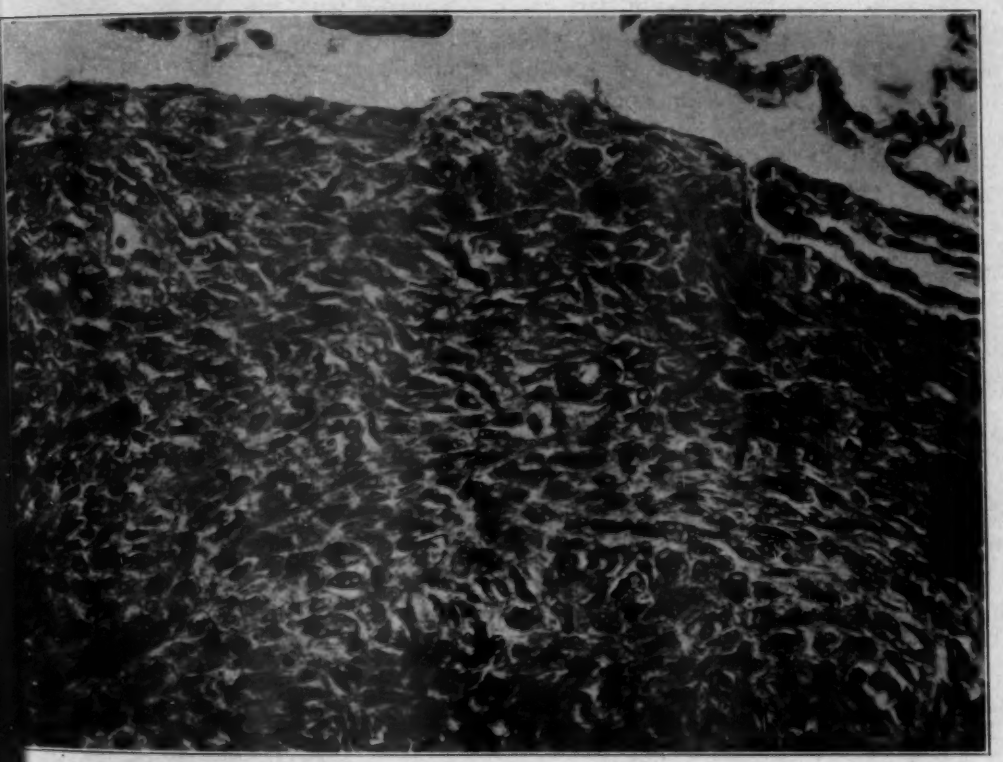

Fig. 9.—Section of metastatic tumor in the lung; × 300.

SUMMARY

The history of a case of telangiectatic osteogenic sarcoma of the humerus is presented and a brief résumé made of the recent literature on osteogenic sarcoma. The most outstanding features of the case were the extreme rapidity of growth of the tumor and the immense size attained by it. Only four months elapsed between the time of the onset of the first symptoms and the death of the patient. The case is discussed briefly from the standpoint of the pathology, diagnosis and treatment.

URETEROCELE *

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Ureterocele, one of the less common abnormalities of the genitourinary tract, is the intravesical bulging of the mucosa of the lower end of the ureter. Kaufmann stated: [1] "If a ureter ends blindly at its vesical end, . . . or if the vesical end of one or both ureters narrows down to an exceedingly fine opening, the end of the ureter covered with vesical mucosa bulges into the bladder like a bubble or cyst, ureterocele vesicalis." Ureteroceles appear as rounded protrusions at one or both ureteral orifices, and, before the days of cystoscopy, they were discovered only post mortem or accidentally in the course of intravesical operations.

DISCUSSIONS IN THE LITERATURE

Historical Observations.—Most of the early observations were made at necropsy, the earliest, according to Patch,[2] by Lechler,[3] in 1835. Civiale [4] mentioned cystic dilatation of the ureter in 1843. Lilienfeld [5] described the first pathologic specimen of the kind in 1856, and in 1862, Smith [6] reported observations on a specimen in which there was bilateral ureterocele. Until 1898, Englisch [7] was able to collect only sixteen authentic cases, and in 1906, Adrian [8] reported fifty-two cases from the literature, mostly accounts of specimens obtained at necropsy.

Apparently the earliest operative intervention for correction of the condition was by Streubel,[9] in 1858. The first excision of ureterocele

* Submitted for publication, Aug. 29, 1929.

* From the service of Waltman Walters, Division of Surgery, The Mayo Clinic.

1. Kaufmann, Edward: Pathology for Students and Practitioners, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 3, pp. 2224.

2. Patch, F. S.: Ureterocele, with Report of a Case, J. Urol. **16**:125, 1926.

3. Lechler, quoted by Patch: J. Urol. **16**:125, 1926.

4. Civiale, quoted by Kreissl and Gehl: Illinois M. J. **37**:315, 1920.

5. Lilienfeld, quoted by Lavandera: Surg. Gynec. Obst. **32**:139, 1921.

6. Smith, T.: Prolapsus of Ureters into Bladder, Tr. Path. Soc. London **14**:185, 1862.

7. Englisch, J.: Ueber cystenartige Erweiterung des Blasenendes des Harnleiters, Centralbl. f. d. Krankh. d. Harn- u. Sex.-Org. **9**:373, 1898.

8. Adrian, C.: Ein neuer, operativ behandelter Fall von intermittirender cystischer Dilatation des vesicalen Ureterendes, Arch. f. klin. Chir. **78**:588, 1906.

9. Streubel, quoted by Patch: J. Urol. **16**:125, 1926.

by suprapubic exposure was by Freyer [10] in 1898. In 1903, Fenwick [11] performed the first transuretheral operation for excision of ureterocele, and Kelly,[12] in 1906, effected a cure by endovesical excision.

Nomenclature.—The nomenclature relative to the condition is most confusing; many terms are used, some of which obviously are inaccurate. Terms encountered in the literature are: cystic dilatation of the lower end of the ureter; cyst of the lower end of the ureteral tube; ureterovesical cyst; cystocele; prolapse of the vesical end of the ureter; prolapse of the ureter; ballooning of the ureteric orifices; ureterocele and vesical ureterocele. Of these, only the last two are considered to be free from serious objections, and Petillo,[13] in a recent discussion, concluded that ureterocele is the best term.

Etiology.—Early reports indicated that ureterocele was more common in young females. It has since become apparent, however, that the condition is found at all ages: the extremes of the ages reported are 4 days and 62 years. The literature seems to indicate that the abnormality is more common in females, although Patch stated that it occurs about equally in the two sexes. In a series of sixteen cases reported by Englisch in 1898, ten were in females; in 1913, Caulk [14] reported six cases, five of which were in females, Martius,[15] in 1927, said: "The condition occurs almost twice as frequently in women as in men." The more recent literature contains many reports of the condition in males, practically all of them adults.

The opinion that ureterocele is based on a congenital abnormality is championed by most of the older and many present-day writers. Papin [16] was convinced that the condition could not be acquired. Of thirteen cases reported by Blumer,[17] ten were evidently of congential origin. Fenwick believed the condition to be dependent on the congenitally blind termination or narrow stricture of the ureteral orifice, and

10. Freyer, P. J.: Obscure Cystic Tumour of the Bladder Containing Two Calculi: Successful Removal by Supra-Pubic Cystotomy, Tr. Roy. Med. & Chir. Soc. **81**:41, 1898.

11. Fenwick, quoted by Michel: Urol. & Cutan. Rev. **25**:726, 1921.

12. Kelly, H. A.: Two Cases of Stricture of the Ureter; Two Cases of Hydronephrotic Renal Pelvis Successfully Treated by Plication, Bull. Johns Hopkins Hosp. **17**:173, 1906.

13. Petillo, Diomede: Ureterocele: Clinical Significance and Process of Formation, Surg. Gynec. Obst. **40**:811, 1925.

14. Caulk, J. R.: Ureterovesical Cysts: An Operative Procedure for Their Relief, J. A. M. A. **61**:1685 (Nov. 8) 1913.

15. Martius, H.: Zur Behandlung der Ureterocele vesicalis, Zentralbl. f. Gynäk. **51**:327, 1927.

16. Papin, E., quoted by Patch: J. Urol. **16**:125, 1926.

17. Blumer, G.: Notes on Two Cases of Ureteral Abnormality, Bull. Johns Hopkins Hosp. **7**:174, 1896.

that the force from above, transmitted to the mucous membrane covering the blind end, or on the weak intramural ureter above a narrowed orifice, causes it to bulge into the cavity of the bladder in the form of a globular cyst. Michel [18] favored Fenwick's theory, but did not think it necessary that the ureter should have an abnormal course through the wall of the bladder, as suggested by Caulk [19] and Bachrach,[20] or that the muscle of the wall of the bladder should be deficient about the ureter. The dilatation of the ureter occurs, he believed, under the mucosa of the bladder, after it penetrates the muscle. Barringer,[21] in discussing the mode of production of ureterocele, said "It is probable that the stricture of the ureteral opening is always congenital."

Thomas and Mellen [22] pointed to the embryonic development of the ureter in supporting the theory of congenital origin. They assumed that failure of development in the renal bud of sufficient lumen at its lower end, as it joins the bladder, may account for the strictured ureteral orifice; also, that the opening which develops in the lining of the bladder may not be large enough.

Petillo, on the other hand, completely discarded the theory of congenital origin of the condition, and ably defended the idea of the acquired nature of ureterocele. Contrary to most writers, he does not believe that stenosis of the ureteral orifice is the cause of ureterocele; he reasons that if it were, the condition would be much more common than it is. In a recent article, he pointed out that a local infection of the lower genito-urinary system, such as seminal vesiculitis, may interfere with the innervation of the vesical end of the ureter, causing nerve block, paralysis and atony, and consequent dilatation of the intramural part of the ureter. Petillo quoted the experimental work of Protopopow to support his theory of local infection as a cause of ureterocele and cited four cases in which ureterocele followed infection of the lower portion of the genito-urinary tract. It is his belief that in the female, pelvic inflammatory conditions could effect the ureter. McKenna,[23] in a paper

18. Michel, L. L.: Ureterocele or Cyst of Lower End of Ureter: A Collective Abstract with Report of a Case, Urol. & Cutan. Rev. **25**:726, 1921.

19. Caulk, J. R.: Description of Two Procedures for the Relief of Obstructions at the Vesical End of the Ureter: Presentation of a High Frequency Cystoscopic Scissor Incisor, J. Urol. **11**:565, 1924.

20. Bachrach, R.: Die Erkrankungen der Harnleiter, in von Lichtenberg, A.; Voelcker, F., and Wildbolz, H.: Handbuch der Urologie, Berlin, Julius Springer, 1928, vol. 5, Spezielle Urologie, p. 1.

21. Barringer, B. S.: Unilateral Kidney Calculus Complicated by Ureterocele of the Opposite Side, Interstate M. J. **20**:343, 1913.

22. Thomas, G. J., and Mellen, D. H.: Bilateral Cystocele or Cystic Dilatation of the Lower End of the Ureters: A Successful Method of Treatment, Minnesota Med. **4**:475, 1921.

23. McKenna, W. F.: Ureterocele, S. Clin. North America **7**:1001, 1927.

published two years ago, defended the theory that the condition is acquired, asserting that dilatation may occur above a stricture following local infection. Lavandera [24] expressed the belief that the condition may result from stenosis following injury from a ureteral stone, from tuberculosis or from any inflammatory process of the ureter. He added, however, "The majority are due to a ballooning of the ureter behind a congenitally stenosed orifice."

The supporters of the theory of congenital origin point to the frequent co-existence of ureterocele and manifestly congenital malformations as additional evidence that the condition is not acquired. Patch estimated that ureterocele is associated with congenital anomalies in about 50 per cent of cases. In thirty-two of the sixty-four cases reviewed by Lavandera the condition was accompanied by anomalies of the genito-urinary system, mainly double ureters. Caillé's [25] case was that of an infant aged 2 weeks, who had double ureters. Spooner and Lindsey,[26] of the Mayo Clinic, reported a case of multiple malformations seen at necropsy in an infant 4 days old. Bostroem [27] Beach,[28] Ogle [29] and Tangl [30] have reported cases of ureterocele associated with anomalies obviously congenital, including abnormalities of the renal pelvis, and ureters, hypospadias, imperforate anus, cleft palate and harelip.

Champions of the theories of congenital and of acquired origin are agreed that the significant factor is the existence of obstruction at the ureteral meatus. Ureterocele was present in two of the five cases of obstruction at the ureterovesical juncture reported by Mertz.[31] Caulk is of the opinion that the obliquity with which the ureter pierces the

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24. Lavandera, M.: Further Observations on Ureteroceles, Surg. Gynec. Obst. **32**:139, 1921.

25. Caillé, Augustus: Prolapse of the Inverted Lower Portion of the Right Ureter Through the Urethra in a Child Two Weeks Old, Am. J. M. Sc. **95**:481, 1888.

26. Spooner, C. M., and Lindsey, Maude L.: Intravesical Ureteral Cyst, Associated with Embryonic Cartilage in the Kidney of a Newborn Infant, J. Urol. **17**:453, 1927.

27. Bostroem, E.: Beiträge zur pathologischen Anatomie der Nieren, Freiburg i. B. and Tübingen, J. C. B. Mohr, 1884, part 1, pp. 48.

28. Beach, Fletcher: Bladder Containing a Pouch Which Opens into a Dilated Coiled Tube (a Third Ureter), Communicating with the Right Kidney by a Smooth Walled Cavity, Which is Shut Off from the Remaining Portion of the Kidney, Tr. Path. Soc. London **25**:185, 1874.

29. Ogle, Cyril: Dilated Ureter and Pelvis of the Left Kidney, with Prolapse of Ureter into the Bladder, Tr. Path. Soc. London **45**:127, 1894.

30. Tangl, Franz: Beiträge zur Kenntnis der Bildungsfehler der Urogenitalorgane, Virchows Arch. f. path. Anat. u. Physiol. **118**:414, 1889.

31. Mertz, H. O.: Congenital Changes in the Urinary Organs as They Influence Pyuria of Infancy and Childhood, J. Urol. **19**:371, 1928.

wall of the bladder is a predisposing factor. The presence of calculi at the ureterovesical juncture, and particularly their presence within the ureterocele sac, has led several writers to the opinion that the obstruction due to the stone was the cause of the condition of ureterocele. Smith described a case which seems to indicate that obstruction by a stone cannot in itself be the cause of the condition. Lavandera, maintaining strict neutrality, pointed out that a congenital condition may exist and may remain symptomless until adult life, when inflammatory changes become superimposed. Thus, ureterocele thought to be due to infection or calculus may have been present since birth, the superimposed inflammatory process precipitating the symptoms. Lavandera is of the opinion that "It is more logical to think of a stone secondary to ureterocele, than the reverse."

Pathology and Associated Pathologic Process.—Although the condition usually is unilateral, it may be present on two sides. Portner,[32] in a series of forty cases, found it bilateral in five. Smith, Burckhart,[33] Rathbun,[34] Aschner[35] and Ryall[36] also reported cases of bilateral ureterocele.

Kaufmann described it as a "bulging into the bladder, like a bubble," and Fenwick described its gross appearance by introducing the word "balloon." The size and shape may vary within wide limits, as pointed out by Patch and others. In early cases there is a small rounded tumor with a broad base, while in the more advanced cases the tumor becomes elongated. The shape varies with the distention; some are described as globular, others as ovoid, triangular or finger-like. The walls of the cyst may be thin, glistening and transparent, or thick, reddened and with dilated vessels coursing over the surface. The position of the ureteral orifice varies: It may be at the usual site, but generally it is eccentrically situated on the side or on the posterior aspect of the tumor. The orifice, however, is almost uniformly constricted.

All authors agree that the wall in ureterocele consists of two layers of mucous membrane; that ureteral mucosa lines the inside, and vesical mucosa, the outer surface. The nature of the tissue between these two mucous surfaces is controversial; some report having found muscular tissue, and others assert that only fibrous connective tissue is present.

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32. Portner, E.: Ueber intermittirende cystische Erweiterung des vesicalen Ureterendes, Monatsbl. f. Urol. **9**:296, 1904.

33. Burckhart, quoted by Michel: Urol. & Cutan. Rev. **25**:726, 1921.

34. Rathbun, N. P.: Bilateral Diverticula of the Ureter, J. Urol. **18**:347, 1927.

35. Aschner, P. A.: Cystic Dilatation of Lower End of Ureters, Internat. J. Surg. **34**:241, 1921.

36. Ryall, E. C.: Operative Cystoscopy, St. Louis, C. V. Mosby Company, 1925, p. 10.

Urinary calculi often are associated with the condition; many writers report the presence of one or more stones of varied sizes. Different types of ureteral and renal pathologic changes may exist. Usually there are thin-walled, dilated or tortuous ureters, and dilated renal pelves, with some degree of hydronephrosis or pyonephrosis. Atrophy of the kidney has been found infrequently. Often some degree of cystitis exists.

Symptoms.—The symptoms presented in ureterocele vary widely with the size and situation of the tumor, and the presence or absence of infection. As has been stated, symptoms may not be present; the condition may be found accidentally. On the other hand, the patient may appear acutely ill, and may suffer severe colicky pain, accompanied by pyrexia and leukocytosis. Many patients with this condition complain of dull, aching pain in the flank, often radiating to the region of the bladder.

Caulk, Hyman [37] and others have classified the symptoms as renal and vesical. The former group are essentially those of obstruction; that is, of hydronephrosis or pyonephrosis, and obtain in cases in which the ureteral orifice is obstructed. Instances in which the opposite ureter was obstructed have been reported. Symptoms referable to the bladder may be only those of cystitis, or if the tumor blocks the urethral orifice, the evidences of obstruction to urinary outflow may be added. Furnival's [38] case is interesting. In a girl, aged 16, the first symptom was sudden discharge of blood from, it was thought, the vagina. At first this was considered to be the onset of catamenia. Later, urinary incontinence, frequency and straining appeared, and the tumor, ureterocele by pathologic diagnosis after removal, was seen presenting at the vulva. In many other early accounts cases were described in which the tumor had passed through the female urethra and appeared at the meatus. This had occurred in four of the cases reported by Blumer; the case of Davies-Colley [39] was that of a girl, aged 18 months, in whom the tumor projected from the urethral orifice.

Diagnosis and Differential Diagnosis.—It is apparent that the diagnosis of ureterocele can be only presumptive save by cystoscopic examination or surgical exploration. There are no pathognomonic symptoms. The tumor may be seen at the usual site of the ureteral orifice, extending into the cavity of the bladder. Hyman warns that it may be overlooked,

37. Hyman, Abraham: Ureterocele with Especial Reference to Endovesical Treatment, Urol. & Cutan. Rev. **22**:435, 1918.

38. Furnival, F. H.: Cystic Dilatation of Lower End of Ureter, Australasian M. Gaz. **23**:394, 1904.

39. Davies-Colley: Specimen of Malformation and Disease of the Ureter and Bladder in a Female Child Eighteen Months of Age, Lancet **1**:372, 1879.

especially if it happens to be empty and collapsed. Young [40] vividly described the characteristic intermittent ballooning of the tumor. Hyman, Caulk, Kelly, McKenna and others have also described and emphasized this ballooning as being characteristic of ureterocele.

Prolapse of the lower end of the ureter is the condition from which ureterocele must be carefully distinguished. The size of the ureteral orifice has been mentioned as a significant point in the differential diagnosis. In prolapse the mucosa is turned out through an enlarged orifice, whereas in ureterocele the orifice is small and the mucosa is not everted. Kapsammer [41] observed that in prolapse the blood vessels appear sharply cut off at the base; in a ureterocele the delicate network of vessels can be seen coursing over the cyst. Other points of difference in the two conditions, as seen by Kreissl and Gehl,[42] are as follows: In prolapse the tumor is pedunculated, the top is broad and the ureteral orifice is situated centrally; in ureterocele the base is broad and the orifice is situated eccentrically. In prolapse, the prolapsed mucosa can be replaced in the ureter, whereas this is not possible if the condition is a ureterocele. Thomas and Mellen called attention to the fact that when filled with urine, a ureterocele sac will transmit light as does a hydrocele sac.

The clinical picture of ureterocele may also resemble that of appendicitis, pelvic infection or disease of the gallbladder, as well as other conditions of the urinary tract with which it may be associated. Benign neoplasms of the bladder must also be differentiated from ureterocele.

Treatment.—The treatment for ureterocele is entirely surgical. In former days suprapubic cystostomy usually was done. The methods of attacking the tumor vary from simple slitting of the cyst, with suture of the two mucous layers, to complete resection and circular suture of the mucosa. Many surgeons still consider the suprapubic route the method of choice, especially in male patients.

According to Patch, the important consideration in the treatment is prevention of ureteral and pelvic stasis. Eisendrath [43] pointed out that the method of treatment must depend on the amount of renal injury, and the presence or absence of infection. If the kidney is injured to such an extent that its function is markedly impaired, and if infection is evident, he chooses to do nephrectomy. Resection of the tumor, with

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40. Young, H. H.: A Case of Intravesical Dilatation or Ballooning of the Ureter, Maryland M. J. **43**:552, 1900.

41. Kapsammer, G.: Ueber cystische Erweiterung des unteren Ureterendes, Ztschr. f. Urol. **2**:800, 1908.

42. Kreissl, F., and Gehl, W. H.: Concerning Cystic Dilatation of the Vesical End of the Ureter with Report of Case, Illinois M. J. **37**:315, 1920.

43. Eisendrath, D. N.: Congenital Stenosis of the Ureter, Surg. Gynec. Obst. **12**:533, 1911.

transplantation of the ureter into the bladder at another point, may be done. Harnagel [44] stated that nephrectomy and ureterectomy have been done without disturbing the cyst. Macalpine reported a case in which he removed the tumor through the opening made at suprapubic cystostomy, with cure.

Many writers have reported excellent results after treating conditions of ureterocele by the transurethral route. Fenwick, in 1903, operated successfully through the urethra. Kelly, Caulk, Wolf,[46] Young, Buerger [47] and many others have accomplished clinical cures by endovesical procedures of various types. Wolf used the cautery of an operating cystoscope to destroy the tumor; Caulk slit the wall of the cyst with vesical scissors; Young used his cystoscopic rongeur to remove the wall of the sac; Buerger introduced a knife and punch forceps through the cystoscope.

Petillo, Martius and Ehrich [48] expressed the opinion that endovesical electro-coagulation is undoubtedly the method of choice. Petillo considered suprapubic cystostomy and resection of the ureterocele as surgical abuse, except under extenuating circumstances. Aschner, Ryall, Brown,[49] Pollet [50] and others also reported good results following transurethral fulguration, and consider this method of treatment adequate and simple. Ehrich considered the only advantage of the suprapubic procedure to be the possibility of doing a bilateral operation in one step.

A number of recurrences after transurethral operation have been mentioned in the literature, but it is the opinion of many writers that these could have been prevented by systematic dilatation of the urethral orifice by means of bougies and catheters. Thomas and Mellen concluded that in mild types of ureterocele the condition can be cured by repeated dilatation of the ureteral orifice, together with pelvic lavage. They emphasize the importance of clearing up all urinary infection, and in their practice, they search for and eradicate all focal infection, such as that of tonsils and teeth.

In 1924, Caulk described his "high frequency scissors," which burn as they cut, to relieve obstruction at the ureterovesical juncture. Later

44. Harnagel, E. J.: A Simple Treatment of Certain Lesions of the Intravesical Ureter in the Female, J. Urol. **10**:141, 1923.

45. Macalpine, J. B.: Case of Ureterocele, Proc. Roy. Soc. Med. (Sect. Urol.) **15**:35, 1921-1922.

46. Wolf, L., quoted by Kreissl and Gehl: Illinois M. J. **37**:315, 1920.

47. Buerger, Leo: Ureteral Obstruction, New York M. J. **105**:909, 1917.

48. Ehrich, E.: Zur Behandlung der Ureterocele, Zentralbl. f. Chir. **54**:3212, 1927.

49. Brown, D. A.: Ureterocele, J. Urol. **16**:363, 1926.

50. Pollet: Cystic Dilatation of Lower End of Ureter, J. d'urol. **11**:15, 1921; abstr., J. A. M. A. **76**:1324 (May 7) 1921.

in the same year, Bumpus [51] described a ureteral scissors designed to cut obstruction at the ureteral orifice, under guidance of the eye.

In 1924, Romaine [52] reported a case in which treatment was by suprapubic cystostomy and excision of a large ureterocele, and in which cure was brought about. He advised against transurethral fulguration for the following reasons: Repeated fulguration would have been necessary; the danger of ulceration of the wall of the bladder was thought to be too great; he feared possible scar formation, with stricture and serious injury to the kidney. Another danger of transurethral operation, as brought out in the literature, is that of postoperative hemorrhage. No such accidents of consequence have been reported, however. Martius warned against intravesical fulguration of the two sides at one operation, because of the temporary interference with the passage of urine that may follow. Ehrich expressed the belief that such procedures must be done in two steps, because obstruction is relieved only after the necrotic eschar has detached itself.

Blum [53] cited a case of ureterocele in which there was a calculus in the sac, and in which the sac ruptured spontaneously, with clinical cure.

This review of the literature was stimulated by two cases in which operation was recently performed at the Mayo Clinic by Walters.

REPORT OF CASES

CASE 1.—The patient was a nulliparous, married woman, aged 25, who had always been well, except for some urinary frequency, until eleven months prior to her visit to the clinic. She then had an attack of severe colicky pain in the suprapubic region; it did not radiate, and was accompanied by nausea, but not dysuria.

When the urine was examined it was reported to contain a great deal of pus; the pyuria persisted during the intervening eleven months. Nothing of significance was discovered on general examination. Urinalysis revealed red blood cells graded 1 and pus graded 4. Tests of renal function showed the right kidney to be functionless. The concentration of urea was estimated at 20 mg. per hundred cubic centimeters of serum. The bladder contained, respectively, 120 and 480 cc. of residual urine on two occasions, and cystoscopic examination revealed a cystic mass, 3 cm. in diameter, with the meatus on the posterolateral aspect, apparently not communicating with the mass. There was chronic diffuse cystitis and right pyelonephritis with atrophy and ureteritis. At examination a few days later, the note was made that although fluctuation in the size of the mass was not seen, the possibility of its being a ureterocele was suggested.

Right nephrectomy was advised; at operation the right kidney was found to be atrophic, and on that side there was duplication of the ureters one of which

51. Bumpus, H. C., Jr.: Ureteral Scissors, J. A. M. A. **83**:1331 (Oct. 25) 1924.

52. Romaine, F. W.: Report of a Case of Cyst of the Left Ureteral Orifice, J. Urol. **11**:489, 1924.

53. Blum, Victor: Die intravesikale blasige Erweiterung und der Prolaps des unteren Harnleiterendes, Arch. f. klin. Chir. **113**:131, 1920.

was the site of a huge hydro-ureter. Nephro-ureterectomy seemed advisable, and accordingly both ureters were severed from the bladder and removed with the kidney. The normal sized ureter was joined to the hydro-ureter in an ampulla-like swelling just before it joined the mucous membrane of the bladder; this measured 2.5 cm. in length, and was dilated to about the same width, bulging into the cavity of the bladder. Above and below this, the ureter was constricted.

At cystoscopic examination nineteen days after operation the cystic tumor in the bladder was reduced to about one-third its former size.

Case 2.—A man, aged 25, five years previously had had acute gonorrheal urethritis. He complained of urinary difficulty, which he had had as long as he could remember, and which consisted of burning, frequency and nocturia, straining, dribbling and voiding of an interrupted stream. He had "always" had soreness in the right flank, but no colic, although at times, when voiding, sharp pain radiated from the bladder upward to the region of the right kidney. Following a siege of influenza four months before coming to the clinic, all urinary symptoms had been aggravated; the attacks of pain in the right flank had become severe, and were accompanied by chills and fever.

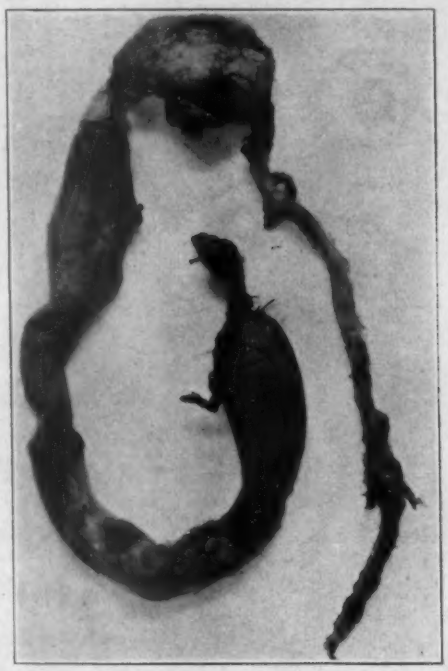

Fig. 1 (case 1).—Right kidney with two ureters, one of which is a hydro-ureter.

On general examination the patient appeared ill. Urinalysis revealed red blood cells graded 1 and pus graded 4. The erythrocyte count was normal, and there was no increase in the number of leukocytes. Blood urea was estimated at 20 mg. per hundred cubic centimeters, and roentgenographic examinations of the kidneys, ureters and bladder gave negative results. The cystogram, however,

revealed a normal outline of the bladder with an egg-shaped filling defect on the right side. On cystoscopic examination, a rounded mass was seen "projecting from the right of the trigone, with broad attachment, smooth, soft, but not translucent; the right meatus was not seen." Functional tests of the two kidneys separately showed that the right kidney was functionless. A diagnosis was made of ureterocele or benign tumor of the bladder, with functionless right kidney, and operation was advised.

On the evening of admission to the hospital, the patient had a severe chill, and the temperature mounted to 103 F., where it remained with but little variation

Fig. 2 (case 2).—Right kidney with hydro-ureter.

for three days, after which it dropped abruptly to normal. During this time, there was intermittent severe pain in the right lower part of the abdomen, radiating up to the region of the kidney, and marked tenderness in the right lower quadrant and flank. The leukocyte count increased from 8,500 to 12,500 cells per cubic millimeter.

After an interval of four days, during which the temperature maintained a normal level, and the leukocyte count returned to normal, suprapubic exploration of the bladder was performed. A huge ureterocele sac was found projecting into the bladder from the region of the right ureteral orifice; the tumor measured approximately 6.5 cm. in length and 3.5 cm. in diameter. The ureteral orifice was seen at its apex. The ureter was about 2.5 cm. in diameter throughout its

upper third; the lower portion was bulbous and measured about 4.5 cm. in diameter. There was hydronephrosis, with destruction of considerable renal substance. The ureterocele was resected, the mucous membrane of the bladder was closed with interrupted sutures of catgut and the ureteral stump was ligated. The ureter was then dissected free from the bladder and freed almost up to the level of the kidney. The suprapubic wound was then closed, with a no. 30 catheter in the bladder and two Penrose cigaret drains in the right perivesical space. The patient was then turned on the left side and the right kidney and ureter were removed intact.

The report of the pathologist included hydronephrosis, with destruction of about 70 per cent of the renal substance, ureterocele and markedly dilated ureter. The patient had an uneventful convalescence and was dismissed from the hospital three weeks after operation in excellent general condition.

COMMENT

In neither of these cases was a positive diagnosis made by cystoscopy. Although ureterocele was considered in each, neither presented the usual appearance of ureterocele at cystoscopic examination; the intermittent ballooning and translucency were absent. The etiology is not clear in either case. In one case, the condition was associated with a congenital anomaly of the urinary tract. In both cases, in all probability, the condition had been present for a longer time than the duration of severe symptoms, which in the first case evidently were due to superimposed infection and in the second to obstruction at both ureteral and urethral orifices. Pyuria had been a persistent symptom in both cases. The radical method of treatment was deemed advisable in view of the infected functionless kidneys and the associated pathologic changes in the ureters. In one case, the ureterocele sac was resected transvesically; in the other it was not disturbed.

CHANGES IN THE HEAD OF THE FEMUR AFTER COMPLETE INTRACAPSULAR FRACTURE OF THE NECK

THEIR BEARING ON NONUNION AND TREATMENT *

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In a discussion of the changes in the head of the femur following a complete intracapsular fracture of the neck, a preliminary consideration of its blood supply is necessary for a proper comprehension of the secondary changes which may take place in it.

It is generally accepted that the main blood supply of the femoral head comes from:

1. The ligamentum teres. Hyrtl,[1] Senn [2] and Langer [3] considered the vessels running through this ligament of little importance and thought that they became obliterated in old people; but recently Schmorl [4] showed in a study of serial sections that the vessels of the round ligament are active even in old age. He cited a case in which, in spite of fracture of the neck of the femur and complete destruction of the capsule, the whole head was adequately nourished through the vessels of the ligamentum teres. This was also proved by Basset [5] and Frangenheim.[6] Frangenheim found permeable although somewhat thickened vessels present in the ligamentum teres of a person 85 years of age. Nussbaum,[7] likewise, was able to demonstrate anastomosis between the arteries of the ligamentum teres and the network of vessels in the head of the femur in a man 60 years old. Iselin [8] proved experimentally that

* Submitted for publication, Sept. 10, 1929.

* From the Department of Surgery, The University of Chicago.

* This work has been conducted under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Hyrtl, J.: Ztschr. f. d. k. Gesellsch. der Aerzte, Wien **1**:58, 1846.

2. Senn, N.: Fractures of the Neck of the Femur, Tr. Am. Surg. A. **1**:1107, 1883.

3. Langer, C.: Ueber das Gefäss-system der Rohrenknochen, Denkschr. d. k. Akad. d. Wissensch. Math.-naturw. klasse Wien. **36**:757, 1865.

4. Schmorl, G.: Die pathologische Anatomie der Schenkelhalsfraktur, München. med. Wchnschr. **40**:1381, 1924.

5. Basset, A.: L'enchevillement sans arthrotomie des fractures du col du fémur; methode du Prof. Pierre Delbet, J. de chir. **17**:81, 1921.

6. Frangenheim, P.: Studien über Schenkelhalsfrakturen und die Vorgänge bei ihrer Heilung, Deutsche Ztschr. f. Chir. **83**:401, 1906.

7. Nussbaum, A.: Die Gefässe am oberen Femurende und ihre Beziehungen zu pathologischen Prozessen, Beitr. z. klin. Chir. **137**:332, 1926.

8. Iselin, H.: Cor.-Bl. f. schweiz. Aerzte **48**:30, 1918.

interruption of the blood vessels in the ligamentum teres does not necessarily lead to serious consequences in the femoral head.

2. The capsular arteries. It is generally agreed that the main vascular supply of the femoral head comes from the branches of the capsular arteries. Schmorl [4] and Nussbaum [7] described the main vessels as being at the upper and lateral parts of the capsule. Frangenheim [6] thought that these vessels are at the anterosuperior aspect of the capsule. Nelidoff [9] found them at the posterior aspect of the capsule. Lexer [10] and Waldenström [11] thought that the lateral two thirds of the head is supplied by capsular branches running along the upper margin of the femoral neck. Another vessel, which supplies only the medial third of the head, is found along the lower margin of the neck. These vessels are also the main source of nutrition for the femoral neck.

From a survey of these anatomic studies it would seem plausible that in an extracapsular fracture, as in the intertrochanteric or peritrochanteric region, when there is preservation of part or all of the capsular attachment, there is absence of, or only negligible interruption of, nutrition from the capsular vessels. On the other hand, a complete medial or intracapsular fracture, especially of the subcapital type, will sever capsular connections and interrupt the main source of blood supply to the head. The head in this case, however, may still be nourished by the vessels of the ligamentum teres and by the synovial fluid. For the satisfactory study of the changes in the femoral head after such a fracture, it is necessary to utilize cases in which there is a separation of the fragments, and others in which there is impaction or contact between the fracture surfaces. Fifteen selected cases have been studied. In the first group, two types of cases will be considered, namely, those in which the head fragment is necrotic, and those in which it is alive in part or whole, and its nutrition adequately maintained by the vessels of the round ligament. In the second group, I shall consider cases in which bony union has not yet occurred, and those in which bony consolidation eventually resulted.

SEPARATION OF THE FRAGMENTS

Cases 1, 2, 3 and 4 are cited to show that, following the fracture the head may subsequently undergo total necrosis, which later is followed by secondary disintegrates and reconstructive changes in it.

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9. Nelidoff, W.: Zur Anatomie des Hüftgelenkes, Verhandl. d. Russ. Chir. Pirogoff. Gesellsch. **5**:16, 1922; Zentralorg. f. d. ges. Chir. **21**:128, 1923.

10. Lexer, F.: Weitere Untersuchungen über Knochenarterien und ihrer Bedeutung für krankhafte Vorgänge, Deutsche Ztschr. f. Chir. **43**:481, 1904.

11. Waldenström, H.: Fractures recentes du col femoral. Traitement operatoire ou orthopedique? J. de chir. **24**:129, 1924.

CASE 1 (NECROTIC HEAD)

Case 1 indicates the possibility of marked secondary vascularization and organization of the greater part of the marrow and a small amount of the dead bone of the necrotic head from the ligamentum teres.

The patient was a woman, aged 54. Two months before examination, she fell on her right hip, following which she received no treatment but had pain and loss of function necessitating the use of crutches in walking. A roentgenogram showed an ununited intracapsular fracture of the neck with considerable erosion of both fragment ends. The head retained its normal density, except in its superior portion and in its inferior portion near the junction with the neck, where the density was slightly reduced. The innominate bone and the distal fragment of the femur showed a slight atrophy from disuse (fig. 1).

Fig. 1 (case 1).—Roentgenogram of the hip, two months after the injury, showing normal density of the greater portion of the femoral head and atrophy of disuse of the innominate bone and distal fragment of the femur.

A Whitman reconstruction operation was performed. The joint cavity was found to be filled with a serohemorrhagic fluid. The neck of the femur showed an intracapsular fracture with complete detachment of the fragments. Most of the neck on either fragment had been eroded away. The sharp edge of the lower part of the distal fragment of the neck fitted into a deep cavity which had been eroded in the under surface of the proximal fragment. In removal of the head, the ligamentum teres tore near the acetabulum, and a spurting artery was seen in the stump, indicating an increased blood supply entering by this route.

Macroscopic Appearance of the Excised Head.—The articular surface of the head of the femur showed a fairly regular hemispherical contour (fig. 2*A*). The surface was covered by bluish-white, glistening articular cartilage. The round ligament was enlarged and hyperemic. Around the fovea, there had been

a small amount of absorption of cartilage and replacement by connective tissue. The fracture surface showed erosion of the neck up to the margins of the articular cartilage, except for a protrusion of dense bone 1 cm. long at its central portion. Beneath this was a cup-shaped erosion, 1 cm. deep, which was produced by the protruding portion of the lower part of the neck. Its surface was hard as a result of the eroded bone dust that had been ground into the cancellous spaces.

A coronal section was made of the head passing through the fovea (fig. 2 *B*). The bone was found to be of normal density and the articular cartilage of normal thickness. The bone was yellowish white in its peripheral portion. But invading the head from the fovea was a dark gray band of tissue extending across the fragment almost to the fracture surface. It appeared to be young connective tissue and blood vessels that had grown in from the round ligament.

Microscopic Appearance.—The articular cartilage was of normal thickness and was attached to the underlying bony cortex, but it was necrotic in its entire

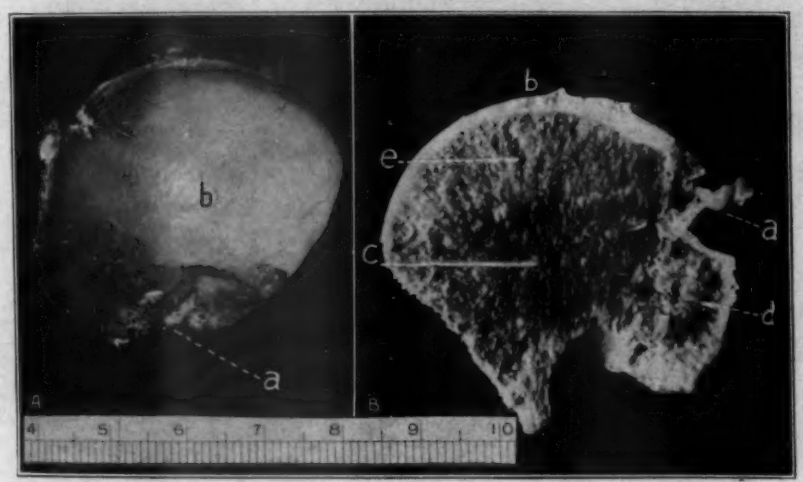


Fig. 2 (case 1).—*A*, appearance of half of the removed femoral head, showing attachment of the ligamentum teres (*a*) and normal contour of the head with slight erosion of the cartilage about the fovea (*b*). *B*, freshly cut section of the head showing a portion of markedly hypertrophied ligamentum teres (*a*), intact articular cartilage (*b*), invading connective tissue (*c*), pinkish spongiosa with fresh bleeding (*d*) and normal bony trabeculae (*e*).

extent (fig. 3). Most of the cartilage cells had broken down, a few showed shrunken, fragmented, poorly stained nuclei. The superficial layer of cartilage immediately surrounding the fovae was eroded and replaced by connective tissue apparently extending from the round ligament, which showed marked hypertrophy and increased vascularity. The deeper layer of the cartilage showed slight calcification. All of the old bone and bone-marrow of the head were necrotic. That in the yellowish peripheral portion, which comprised approximately one third of the specimen, remained uninvaded, and its trabeculae were of normal size. In the dark central zone, the necrotic marrow had been absorbed and replaced by vascular young connective tissue, fat and fibroblasts. A very small amount of new bone

was being laid down in the connective tissue and on the old necrotic trabeculae, and in places the old bone was being absorbed (fig. 4). These bone lamellae lay in a matrix of loose fibrous connective tissue containing many dilated blood vessels and densely infiltrated with red blood cells, osteoblasts and hemopoietic cells. This highly vascularized tissue replacing the dead marrow formed a more or less diffused zone which extended from the ligamentum teres to the fracture surface below in the region of the eroded pit and peripherally to near the junction of bone and cartilage at the rim of the femoral head. The deep crypt on the fracture surface was lined by small fragments of dead bone that had been ground into the cancellous spaces by pressure from the opposing bone. In places, these fragments were surrounded by vascular connective tissue, and showed new bone formation and lacunar absorption.

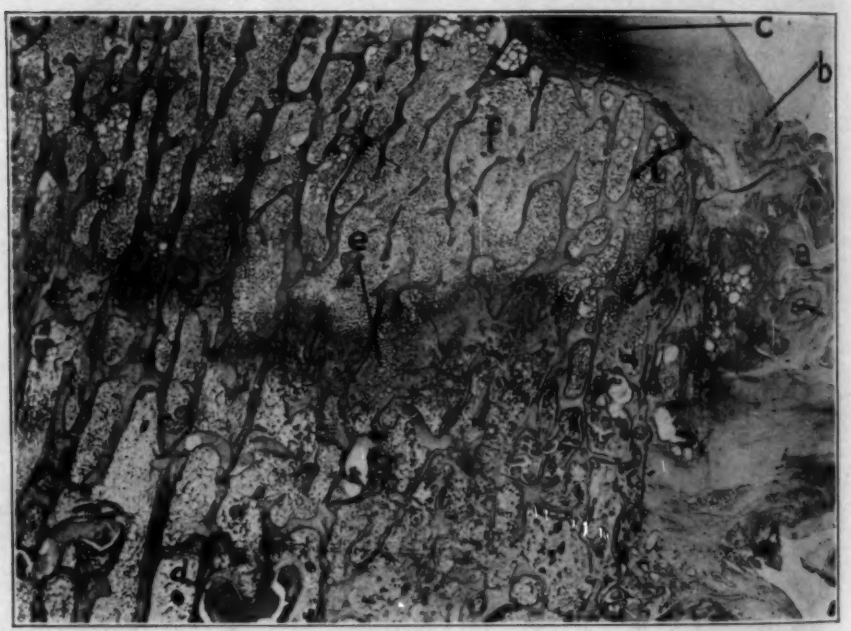


Fig. 3 (case 1).—Area of attachment of the ligamentum teres. Note ligamentum teres with numerous blood vessels (*a*), fibrous tissue invasion of the cartilage (*b*), slightly calcified cartilage (*c*), numerous dilated blood vessels in the marrow (*d*), highly vascularized fibrous marrow (*e*) and degenerated and unreplaced marrow with necrotic bony trabeculae (*f*). Reduced from a magnification of × 60.

Summary.—Summarizing the case, one has:

1. Nonunion of an intracapsular fracture of the neck of the femur of two months' duration with apposition of the fragments.

2. Very little decrease in the density of the head, but atrophy of disuse of the distal fragment and pelvis.

3. Necrosis of the entire head, including bone, cartilage and bone-marrow.

4. Invasion of about two thirds of the cancellous space of the necrotic head by vascular connective tissue extending from the fovea across the central portion to the

fracture surface; very slight bony transformation going on in this region as a result of absorption of the old necrotic bone and replacement of it by newly formed bone.

5. Marked hypertrophy and vascularization of the ligmentum teres.

6. Slight erosion of the articular cartilage with fibrous tissue replacement about the fovea.

CASE 2 (NECROTIC HEAD)

Case 2 also showed secondary invasion of the necrotic head by vascular connective tissue from the region of the ligamentum teres with subsequent absorption of the necrotic lamellae and formation of a small amount of new bone in this region. Marked erosion of the

Fig. 4 (case 1).—Area of regenerative and absorptive processes. Note newly formed bone (*a*), osteoblast (*b*), dilated blood vessels (*c*), multinucleated giant cell (*d*) and necrotic bony trabeculae (*e*). Reduced from a magnification of × 160.

articular cartilage and underlying spongiosa about the fovea occurred in this head.

The patient was a woman, aged 57. Sixteen months before examination, she fell on her right hip, and thereafter suffered marked pain and disability in it. A roentgenogram at that time showed an intracapsular fracture of the neck of the right femur. A closed reduction was performed on the same day, and the body and extremity were placed in a long plaster spica, which remained on for eight weeks. The cast was then removed, but on account of the persistent disability and pain in the right hip, she remained in bed for five months. After that, she walked on crutches. The roentgenogram showed nonunion, with complete erosion of the

neck fragments. The head cast a shadow of normal density, except for a narrow margin about the fovea, where it was reduced (fig. 5). The distal fragment and innominate bone showed atrophy of disuse.

A Whitman reconstruction operation was performed. The fragments were found separated with the head lying in the acetabulum and the end of the distal fragment displaced upward. The ligamentum teres was small, and no spurting artery was seen when the head was removed. The neck portion had been completely eroded, and the fracture surface was largely covered by an overgrowth of connective tissue from the capsule.

Macroscopic Appearance of the Excised Head.—The fovea was occupied by a narrow ligamentum teres, which readily tore out from its attachment to the head. The head showed an almost normal contour, except for an area 2 cm. in diameter about the enlarged fovea, where a depression was encountered (fig. 6*A*). In this region, the articular cartilage and the subchondral bone were eroded, exposing a

Fig. 5 (case 2).—Roentgenogram of the hips. Note the marked absorption of the neck of the right femur. The head cast a dense shadow, except for a small invaded area at the fovea, which showed reduction in density.

dark-staining spongiosa. The rest of the articular surface of the head was covered by whitish, glistening cartilage. The fracture surface was lined by small fragments of bone to which a small amount of fibrous tissue was adherent.

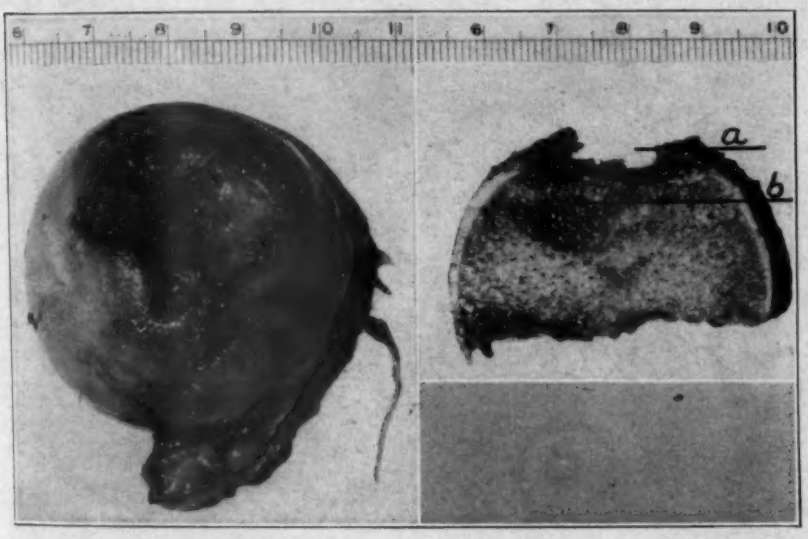
The femoral head cut with normal resistance. The cut surface showed the defect at the superior portion of the head (fig. 6*B*). This was lined by a darkly stained tissue, which extended down into the underlying spongiosa. The rest of the spongiosa was yellowish. The articular cartilage was intact, except at the margin of the erosion about the fovia, where it was lifted and undermined by the darkly stained spongiosa.

Microscopic Appearance.—The articular cartilage was necrotic and showed marked calcification in the deeper layer (fig. 7). Most of the cartilage spaces were empty, while a few were occupied by small, shrunken, poorly staining cells. At the margin of the erosion about the fovea, the cartilage was lifted and undermined by an ingrowth of vascularized connective tissue. Lining this erosion and

extending down deep into the spongiosa was a rather loose, cellular, vascularized connective tissue. Embedded in this, especially along the floor of the erosion, were necrotic bony trabeculae which showed simultaneous absorption and formation of new bone. Red blood cells, monocytes and osteoblasts were also seen about the necrotic lamellae. Immature fibroblasts pushed their way from the invading vascularized connective tissue into the surrounding necrotic fatty marrow. This gradually merged into a clear area away from the fovea and along the fracture surface, where the necrotic bony lamellae showed no signs of absorption or regeneration. They were surrounded by a dead marrow made up largely of fat spaces.

Summary.—The case may be summarized as follows:

1. Intracapsular fracture of the neck of the femur with wide separation of the fragments.



A B

Fig. 6 (case 2).—*A*, appearance of the femoral head showing the erosion about the fovea. *B*, freshly cut surface of the femoral head showing erosion (*a*) and invaded and vascularized portion (*b*).

2. Normal density of the head, except for slight rarefaction in its superior half; marked absorption of the neck. Atrophy of disuse of the distal fragment and of the innominate bone.

3. Necrotic femoral head.

4. Presence of a ligamentum teres.

5. Invasion of the necrotic head by vascularized connective tissue from the fovea downward into the upper half of the fragment.

6. Marked absorption of the articular cartilage about the fovea.

7. Formation of a very small amount of new bone and bone-marrow and absorption of old necrotic bone in the secondarily vascularized region.

CASE 3 (NECROTIC HEAD)

Case 3 is cited to indicate that the superior portion of the necrotic head pressing against the acetabulum may be traumatized and the cartilage and bone thereby undergo extensive destruction. Secondary invasion of the necrotic head from the ligamentum teres and surrounding capsule may occur with simultaneous absorption of dead bone and formation of new bone.

The patient was a woman, aged 44. Thirteen months before examination, she fell on her right hip and subsequently suffered pain and limitation of motion at

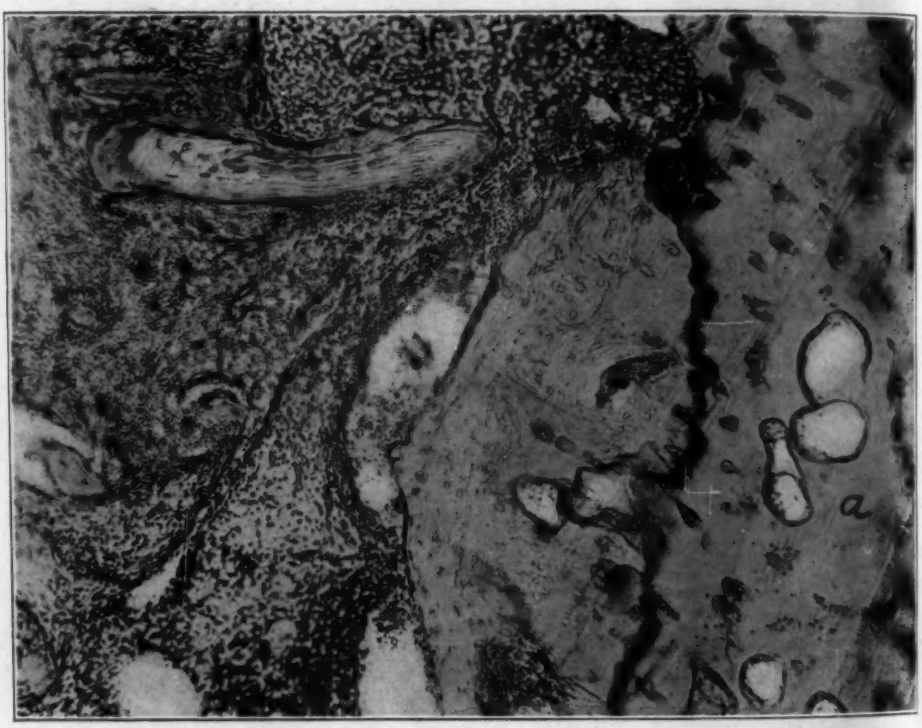


Fig. 7 (case 2).—Microscopic section of the invaded portion of the head. Note necrotic articular cartilage (*a*), markedly vascular and fibrous marrow (*b*) and new formed bone on a necrotic trabecula (*c*). Reduced from a magnification of × 160.

the hip. The roentgenogram taken of the hip at the time showed an intracapsular fracture of the neck with separation of the fragments. A closed reduction was attempted, and a long plaster of paris spica applied. This remained in place for ten weeks. Walking thereafter, although possible, produced pain in the right hip. Roentgen examination at this time showed nonunion with a separation of the fragments and marked absorption of the neck (fig. 8). The head cast a dense shadow which was uniform except in its lower portion where it is reduced. The neck showed marked rarefaction and absorption. This was verified when on

the day after the examination a Whitman reconstruction was performed. At the operation, the head was found embedded in fibrous tissue adhesions in which the ligamentum teres could hardly be identified. It was considerably damaged in prying it out of the acetabulum and a portion was detached bordering on the fovea.

Macroscopic Appearance of the Excised Head.—The articular cartilage showed marked irregularity with destruction at the superior surface, where there was a defect from injury inflicted during removal and from absorption at the point of attachment of round ligament about 2 cm. in diameter (fig. 9). The underlying spongiosa in the superior portion was exposed, irregular and fragmented. On the outer circumference of the head there was more of the cartilage that could be seen. Only a narrow strip of fibrous tissue, the remains of the round ligament, was found attached at the fovea. The fracture surface was free from adhesion. It was lined by hard, bony trabeculae, which stood out prominently.

Fig. 8 (case 3).—Roentgenogram of the hip showing almost no reduction of density of the femoral head, but marked atrophy of disuse of the distal fragment and the pelvis.

On sawing, the head cut with normal resistance. The cut surface showed a large triangular area devoid of cartilage and subchondral bone in the region of the attachment of the ligamentum teres (fig. 10). Extensive and more marked gross destruction and disorganization of the cartilage and underlying spongiosa were seen at one of the osteochondral junctions. In the spongiosa, columns of grayish, soft tissue ran from the articular surface toward the fracture line.

Microscopic Appearance.—The entire remaining articular cartilage was necrotic and was much thinned at its margins and along the anterior surface. The remnants of the cartilage showed empty cartilage spaces and marked calcification in the deeper layer. While this remaining cartilage was intact along one region of the osteochondral junction, it was detached and fragmented in another with invasion by fibrous tissue. The triangular defect at the superior surface showed also a disappearance of a part of the underlying spongiosa. The sides and apex of this defect were made up of necrotic fragments of bony lamellae lying in a matrix of

dense, practically acellular and avascular fibrous connective tissue similar to that which made up the soft, grayish columns extending from the articular surface to the fracture surface of the head. Signs of absorption of bone and formation of new bone were nowhere to be seen in this region. The detachment, marked destruc-

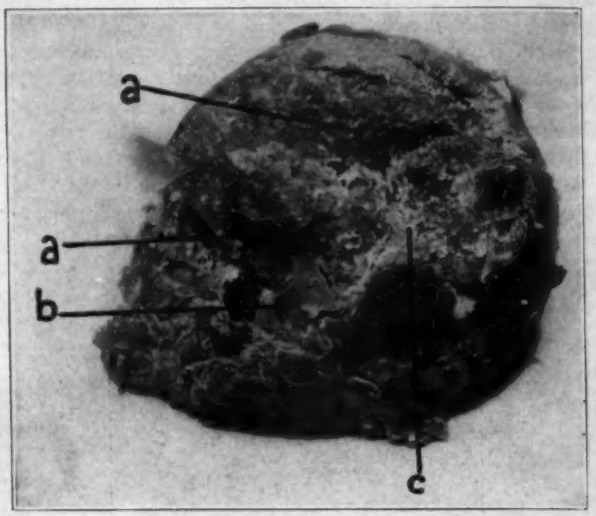


Fig. 9 (case 3).—Appearance of the removed femoral head. Note areas of erosion (*a*), remains of the round ligament (*b*) and fibrous tissue (*c*).

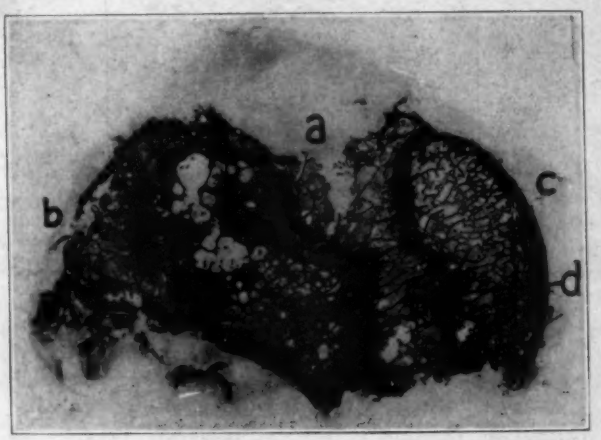


Fig. 10 (case 3).—Photomicrograph of a section showing defect from erosion and from injury during removal (*a*), region of marked destruction of cartilage and bone (*b*), necrotic but intact cartilage and underlying bone (*c*) and columns of invading fibrous tissue in the spongiosa (*d*).

tion and fragmentation of the articular cartilage and the underlying bony lamellae in one portion of the specimen gave a picture of marked traumatic erosion. Highly vascular connective tissue invaded this area, throughout which hemopoietic and

fatty marrow, a small amount of new bone and active absorption of old and necrotic bony lamellae were encountered (fig. 11). At about the osteochondral junction, invasion of the calcified layer of the cartilage by the underlying fibrous marrow with formation of new bone was taking place. In between the columns of dense, scarlike connective tissue, the marrow was degenerated and contained numerous large, empty spaces. In the deeper levels, one encountered scattered areas of calcification.

Summary.—Summarizing the case, one has:

1. Intracapsular fracture of the femoral neck with separation of the fragments.

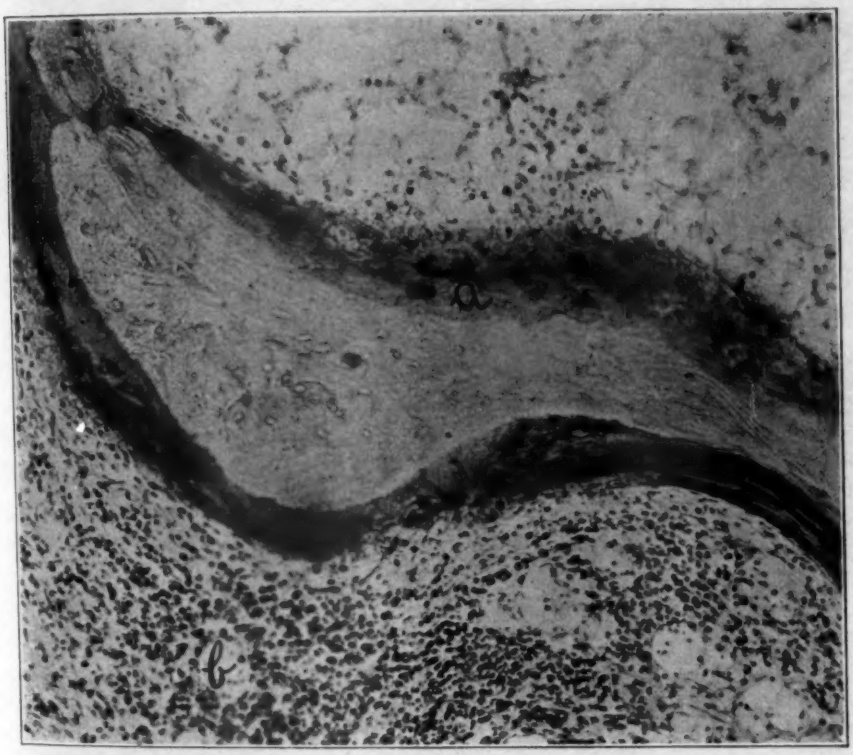


Fig. 11 (case 3).—Section of a necrotic bony trabecula showing newly formed bone about it (*a*) and vascular and cellular marrow (*b*). Reduced from a magnification of × 160.

2. Roentgenogram disclosing dense head with atrophy of the innominate bone and distal fragment of the femur.

3. Marked absorption of the neck.

4. Totally necrotic femoral head.

5. Invasion from the round ligament of about one-half of the necrotic head by vascularized connective tissue which remained fibrous in its peripheral portion and differentiated into bone marrow in its older central portions. Fragmentation of the cartilage and bone in the upper or traumatized portion of the head.

6. Active absorption of necrotic bone and formation of a small amount of new bone in the region invaded by young vascularized connective tissue.

7. Areas of calcification near the fracture surface.

CASE 4 (NECROTIC HEAD)

Case 4 is cited to show that although the ligamentum teres is present the head may undergo necrosis after its separation from the distal fragment and may fail to be secondarily vascularized by it. In such instances, when the neck is necrotic and eroded, nonunion in spite of good apposition of the fragments may occur. Secondary degenerative changes appear in the head.

Fig. 12 (case 4).—Roentgenogram of the hip, showing nonunion of the fracture a year after closed reduction of the fragments. Note the marked absorption of the neck and the dense head with a small area of rarefaction at the fovea.

The patient, a woman, aged 48, one year before examination fell on her right hip and subsequently began to have pain and marked limitation of motion at the hip. Two days after the accident, she started to walk again but with pain in the hip. The roentgenogram taken two weeks later showed a complete intracapsular fracture of the neck of the femur with separation of the fragments. With the patient under ether anesthesia, a closed reduction was attempted. Four months of immobilization in a plaster of paris spica followed. The cast was then removed, and the patient was allowed to walk with crutches. She still complained of slight pain in the right hip. Roentgen examination showed that the fragments

were in a fairly good position, but nevertheless nonunion had resulted (fig. 12). The head cast an almost normal shadow as contrasted with the marked diffuse decrease in density and marked absorption of the neck of the femur. A Whitman reconstruction operation was performed. At operation, the fragments were found in good apposition, and in removal of the head a narrow ligamentum teres had to be cut.

Macroscopic Appearance of the Excised Head.—The head had a fairly normal spherical contour, except for slight flattening at the superior surface about the fovea (fig. 13*A*). This region was marked by a loss of cartilage and underlying spongiosa, causing an erosion about 1 cm. in diameter. The articular cartilage was clear, whitish and glistening and was slightly undermined about the erosion. The ligamentum teres was made up of a narrow strip of fibrous tissue which easily tore out from its attachment to the head. Areas containing hard spicules of bone were found along the irregular fracture surface. The neck portion of the distal fragment was slightly absorbed, and the interior was occupied by dark, soft, granular marrow containing numerous small pieces of bone.

The femoral head cut with normal resistance. The articular cartilage was intact, except at the region of the fovea, where it was eroded (fig. 13*B*). The

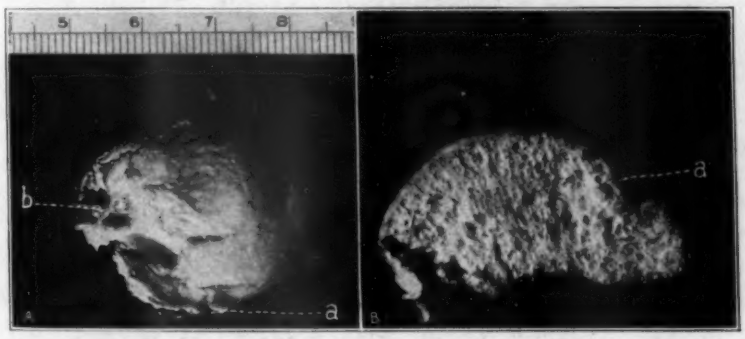


Fig. 13 (case 4).—*A*, photograph of half of the femoral head. Note remains of the ligamentum teres (*a*) and an area of erosion in the articular cartilage and the underlying spongiosa (*b*). *B*, cut surface of the femoral head, showing the area of erosion (*a*).

remaining cartilage was adherent to the subchondral bone and varied in thickness from 1 to 3.5 mm. The spongiosa had a uniform yellowish, granular appearance.

Microscopic Appearance.—The head was necrotic. In the region of the fovea, an area of the cartilage, 1 cm. in diameter, was eroded, exposing the underlying bony lamellae, which were necrotic and fragmented. A narrow band of fairly vascular connective tissue, presumably extending from the fovea, was seen along the joint surface of the articular cartilage (fig. 14). This band, however, had not invaded the spongiosa. Although the remaining cartilage was adherent to the subchondral bone it was necrotic, showed absence of cells and was thin immediately about the erosion. This thinning was due to erosion of the superficial layer by pannus-like connective tissue from the fovea, and to absorption of the deep calcified layer as a result of invasion by the subchondral marrow. This latter process undermined the cartilage in places and lifted it up from the underlying subchondral bone. The bony lamellae everywhere were necrotic, and lay in a matrix of degenerated marrow containing red blood cells and numerous large

empty spaces. No signs of absorption of the necrotic bone or formation of new bone could be seen in the spongiosa.

Also of interest were the changes in the neck portion of the distal fragment. They presented a picture of necrosis and absorption. The cancellous spaces were markedly dilated. This dilatation was especially marked about the fracture surface, where the spaces contained a decided increase in fat with a comparatively small amount of lymphoid and fibrous tissue. Embedded in this marrow were small, thin-walled blood vessels which had few red blood cells in the lumen. The bony lamellae in this region were necrotic and markedly diminished in size and number. Along the fracture surface, these were reduced to such a degree that only occasional pieces of bone were encountered. An active absorptive process was going on along the periphery of the neck bordering the fracture surface. Here one

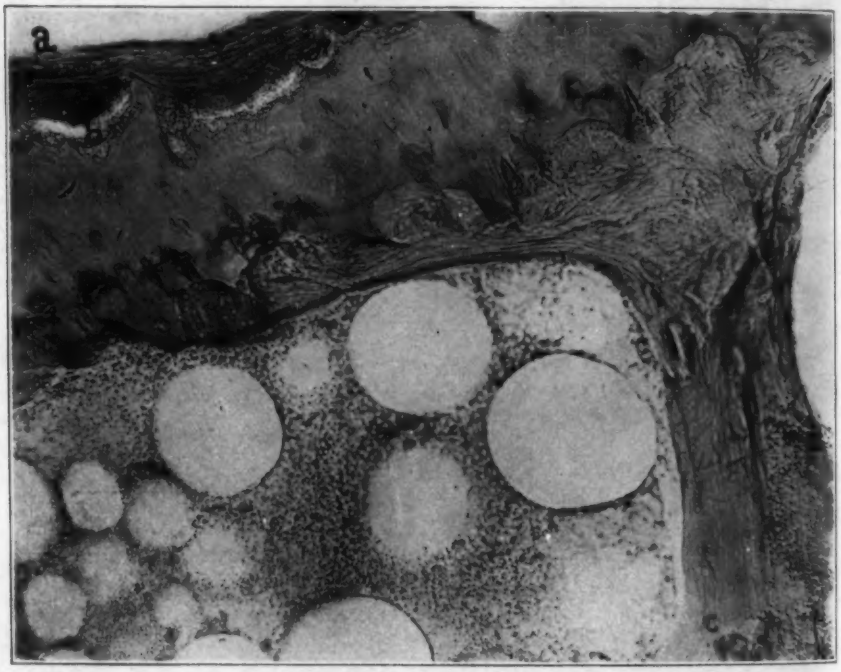


Fig. 14 (case 4).—Section of the articular surface showing vascular connective tissue extending from the fovea (*a*), cartilage erosion (*b*) and necrotic bony trabecula (*c*). Reduced from a magnification of × 80.

encountered spaces filled by young vascularized connective tissue infiltrated with numerous multinucleated giant cells, red blood cells and a few monocytes. Where these were present there was active and extensive lacunar absorption of the bone. No formation of new bone was seen along the fracture surface. Further down the neck, this merged into a region that presented a picture of partial necrosis. Well staining bone cells still persisted around the haversian canals, although the compact portion of the bone or the region of the intermediate lamellae was marked by their absence leaving dilated and empty lacunae.

Summary.—The case may be summarized as follows:

1. Early reposition of the fragments, which nevertheless resulted in nonunion

2. Normal density of the head, as shown by the roentgenogram with erosion of the neck.

3. Totally necrotic femoral head with failure of vascularization from the ligamentum teres.

4. Erosion of the articular cartilage about the fovea with destruction and fragmentation of the underlying bony lamellae.

5. Failure of absorption of bone, and of formation of new bone in the spongiosa.

6. Erosion and necrosis of the neck portion of the distal fragment.

COMMENT ON CASES OF NONUNION IN WHICH HEAD BECAME NECROTIC

As may be noted from the descriptions of the specimens, all the femoral heads became necrotic after the fracture. The ligamentum teres was found intact in every instance and showed varying degrees of development. Except in case 4, proliferating connective tissue proceeding from the region of the fovea was seen invading the articular cartilage and spongiosa of the head. These changes show that although the round ligament is present, a separated femoral head, owing to insufficient nourishment, may undergo necrosis after complete intracapsular fracture of the neck of the femur; and that secondary vascularization of the head from it may or may not occur. On the other hand, the round ligament may be well developed and its vessels may penetrate even the deeper layers of the spongiosa, as in cases 1 and 2, or young proliferating connective tissue may gain entrance either through the fovea (Bonn) or through adhesions along the surface of the eroded neck or articular cartilage, as in case 3, and invade the spongiosa. Consequently, varying degrees of secondary vascularization and organization of the head occur. In cases in which this vascularization is marked and extensive, an organization or replacement of the necrotic head and efficient nourishment of the greater part of the head allowing active formation of new bone may result. This is well illustrated by cases 1 and 2, in which a transformation and partial organization of two thirds and one half of the heads, respectively, occurred after the injury. The activity of such revascularization varies greatly in different cases. In case 1, a transformation of the necrotic marrow and to a very slight extent of the necrotic bone of nearly two thirds of the head occurred within a period of two months; in case 2 similar organization of one half of the head had resulted by the end of sixteen months. Hess previously showed that the ligamentum teres frequently contains large arteries that penetrate into the spongiosa of the head until late in life. These vessels may so proliferate as not only to organize and preserve considerable parts of the femoral head, but also to permit an active regeneration of bone. The bone apparently forms by metaplasia of the invading fibroblasts or angioblasts as advocated by Petrow and Baschkirzew for the replacement of the necrotic bone in a transplant. However, some of it may come from osteoblasts surviving about the fovea.

Necrosis of the femoral head following complete intracapsular fracture of the neck of the femur has been known since the time of Sir Astley Cooper, nearly one hundred years ago. In 1896, Köcher [12] and more recently Axhausen [13] and Bonn [14] expressed the opinion that every subcapital fracture of the neck results in necrosis of the head.

The possibility of secondary vascularization of a necrotic head was less well known until the recent studies of several investigators, prominent among whom were Schmorl,[4] Hesse [15] and Bonn.[14] It was from the work of these observers that secondary vascularization of the necrotic head became recognized. The first two authors believed that the ligamentum teres itself proliferates and causes the revascularization of the head. They observed it to be so well developed even in advanced age that not only a revasculization and replacement of considerable portion of the necrotic head but also an active regeneration of bone and some callus formation often occurs. Bonn, however, after studying several preparations of femoral heads following intracapsular fracture of the neck of the femur, stated that the ligamentum teres is important for the nutrition or revascularization of the head only in that it serves as the portal of entry for proliferating connective tissue to penetrate and invade the spongiosa and replace the necrotic head.

Necrosis of the head, partial or complete, predisposes to secondary transformative changes in it. This is a common occurrence in necrotic structures as in free bone and cartilage transplants, which appear to have markedly reduced resistance to any kind of injury and invasion by fibrous connective tissue. If the necrotic head fails to be secondarily vascularized from the ligamentum teres, simple destruction and fragmentation of the articular cartilage and the underlying bony lamellae occur in the traumatized region. This structural disorganization is seen more in the region that received the greatest amount of injury. If an active invasion of the head by a pannus-like connective tissue extending from the ligamentum teres occurs, there is apt to be an early erosion with replacement of the cartilage and bone about the fovea. This erosion serves subsequently as the portal of entry into the spongiosa for proliferating connective tissue. The deep layer of the remaining articular cartilage is then attacked and gradually absorbed from the interior by the subchondral fibrous marrow with or without formation

12. Kocher, T.: Beiträge zur Kenntnis einiger praktisch wichtiger Frakturformen, Basel und Leipzig; Forms Hfts. 10, 11 and 12, 3. R., of: Mitt. a. Klin. u. med. Inst. d. Schweiz, 1895-1896, p. 585.

13. Axhausen, G.: Die Nekrose des proximalen Bruchstüchs beim Schenkalhalsbruch und ihre Bedeutung für das Hüftgelenk, Arch. f. klin. Chir. **120**:325, 1922.

14. Bonn, R.: Zur Frage der knöchernen Heilung subkapitaler Schenkelhalsfrakturen, Arch. f. klin. Chir. **134**:270, 1925.

15. Hesse, F.: Zur pathologischen Anatomie der Schenkelhalsfrakturen, Arch. f. klin. Chir. **134**:141, 1925.

of new bone in the cartilage layer. Even an actively revascularized and considerably organized necrotic head undergoes secondary degenerative changes following traumatism, as from rubbing together of fragment ends and invasion by proliferating connective tissue.

In case of nonunion the head has relatively little stress thrown upon it as it participates but little in weight-bearing. However, there may be enough pressure against it from the distal fragment to erode the neck and to break down bony trabeculae and necrotic cartilage at the point of greatest pressure against acetabulatum. The very slow rate of absorption of necrotic portions and replacement by new bone results from this disuse. Hence the dead head may cast a heavier shadow than the surrounding bone for two or three years before it is transformed. Functional stimulation is essential for rapid revascularization absorption and transformation when the conditions for the invasion of blood vessels are favorable. Its influence will be shown later in cases reported in which bony union occurred in the presence of a necrotic head and transformation took place more rapidly.

CASE 5 (LIVE HEAD)

A femoral head, however, which becomes completely separated after an intracapsular fracture of the neck of the femur may, instead of becoming necrotic, be preserved and kept alive by an adequate nourishment from the vessels of the ligamentum teres. Case 5 is cited to indicate that the separated head may remain alive and be adequately nourished by the vessels of the ligamentum teres and, when the fracture is recent, it may show only slight atrophy subsequent to the loss of function. Gross destruction of the cartilage and bone generally fails to occur, although beginning invasion and replacement of the deeper layer of the articular cartilage at its superior portion by the subchondral fatty marrow may be encountered.

The patient was a man aged 60. Sixteen months before the examination, he was struck on the right thigh by the fender of an automobile. He had pain and loss of function of the hip and remained in bed for thirty-three days at which time a roentgenogram was taken which was reported to show nonunion of a fracture of the neck of the femur. Reduction with the patient under ether anesthesia was performed, and the leg was kept immobilized with weight extension for ten weeks. He was then allowed to be up and about on crutches. Another roentgenogram was taken on the day of admission, and this showed nonunion and erosion of neck fragments. The head revealed a slight diffuse decrease in density (fig. 15). A Whitman reconstruction operation was performed. At operation, the ligamentum teres was found intact. There was a cavity between the fragment ends and adhesions between the margins of the head fragment and the surrounding capsule.

Macroscopic Appearance of the Excised Head.—The head showed a normal spherical contour (fig. 16). The articular cartilage was intact and showed no loss of substance. It was smooth, clear, yellowish and glistening. A small ligamentum teres was found attached at the fovea. The fracture surface was irregular and covered by a fibrous layer beneath which was a newly formed layer of bone.

The head cut with decreased resistance. The cut surface revealed an intact articular cartilage which varied from 3 to 5 mm. in thickness. The spongiosa was increased in amount and had a uniform yellowish, trabeculated appearance.

Microscopic Appearance.—From a general survey of the head, it was found to be alive. The articular cartilage was normal, except for slight calcification

Fig. 15 (case 5).—Roentgenogram showing a diffuse decrease in density of the head of the right femur.

Fig. 16 (case 5).—Appearance of the femoral head showing normal contour and intact articular cartilage.

of the deep layer and the presence of a thin layer of perichondral fibrous tissue along its joint surface about the fovea. The cartilage cells were present and stained well. At the superior surface about the region of the fovea, the articular

cartilage was invaded from the interior by the subchondral fatty marrow, forming marrow cavities and vascular spaces in the cartilage (fig. 17). With the encroachment of the subchondral marrow, there was a simultaneous replacement and thinning of the articular cartilage in this region. These chondral marrow cavities contained fat cells, blood vessels, red blood cells, few monocytes and multinucleated giant cells. Strips of newly formed lamellar bone could be found partially lining these cavities. Although the bony trabeculae showed considerable diminution in number and size, they still retained normal-appearing bone cells (fig. 18). These lamellae lay in a matrix of markedly fatty marrow containing a few blood vessels, red blood cells and monocytes. Only in a small region at the fracture surface did this fatty marrow merge into a limited zone of slightly vascular connective tissue. Embedded in this tissue was a small amount of newly formed

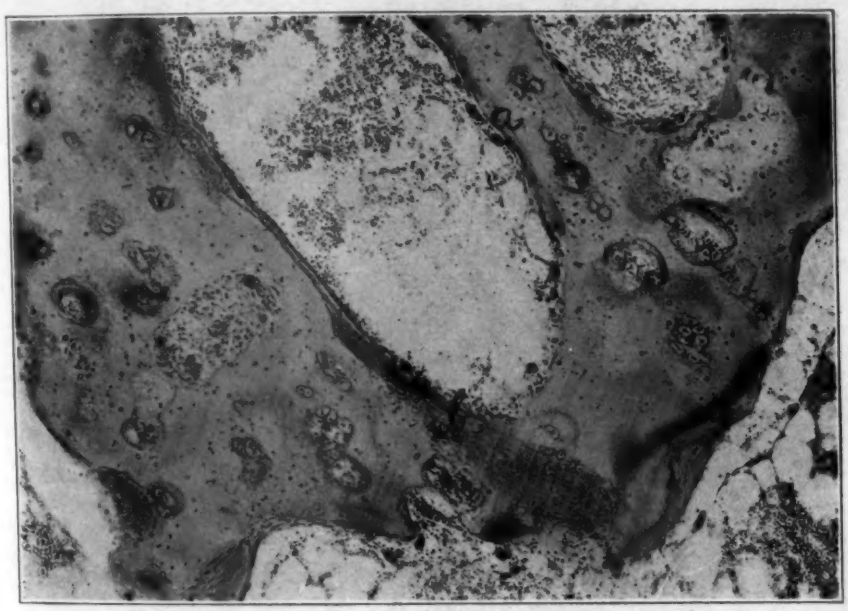


Fig. 17 (case 5).—Invasion of cartilage by the subchondral fatty marrow and vascular spaces, showing multinucleated giant cells (*a*) and newly formed lamellar bone (*b*). Reduced from a magnification of × 80.

bone surrounded by many osteoblasts. Despite the presence of this vascularized connective tissue, no evidence of absorption of bone was seen in the proximal fragment. A synovial covering was present over a portion of the fracture surface bordering on the cavity.

Summary.—The case may be summarized as follows:

1. Nonunion of fracture of the neck with erosion of the fragments of sixteen months' duration. Diffuse decrease in density of the head.

2. Living, although atrophied head fragment, with slight formation of new bone at one end of the fracture surface.

3. Intact ligamentum teres.

4. Invasion and replacement of the slightly calcified deeper layer of the superior portion of the articular cartilage by the subchondral marrow, with formation of narrow strips of new lamellar bone about the marrow cavities thus formed.

CASE 6 (LIVE HEAD)

Case 6 indicates the marked atrophic change that a separated but live head of the femur may undergo after four years. A marked replacement and thinning of the superior portion of the articular cartilage due to invasion by the subchondral marrow are noted.

The patient, a woman, aged 58, four years before examination fell on her left hip. Subsequently, the hip became so painful that weight bearing and movement

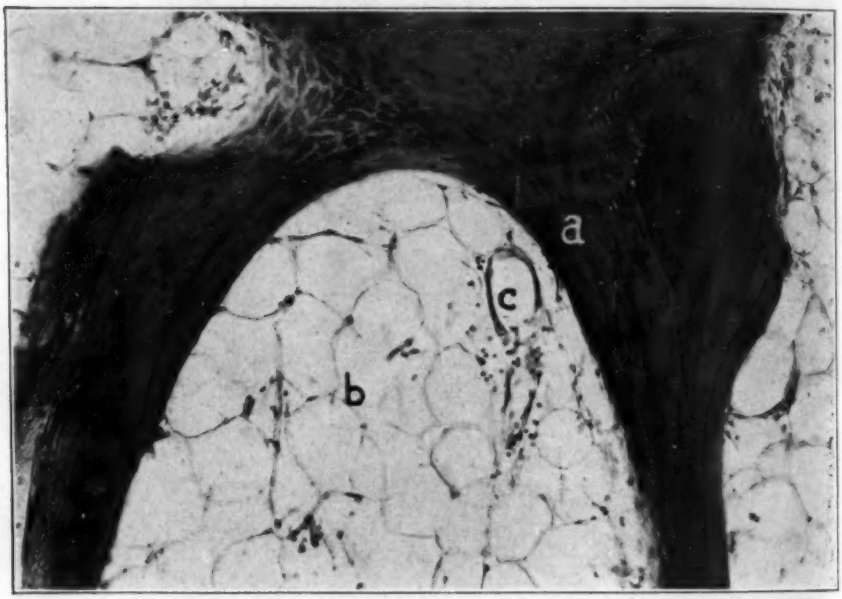


Fig. 18 (case 5).—Section of the spongiosa showing living bone trabecula (*a*), dilated fatty marrow cavity (*b*) and blood vessels (*c*). Reduced from a magnification of × 160.

were impossible. A closed reduction with the patient under ether anesthesia was performed four days after the injury. Nine months of immobilization in a plaster of paris cast followed, without improvement. Treatment was finally discarded, and from then until the time of the operation the patient used crutches. A roentgenogram of the hip at the time of examination showed an old intracapsular fracture of the neck of the femur with complete erosion of the fragments of the neck (fig. 19). The head revealed considerable diffuse decrease in density. A Whitman reconstruction operation was performed, and the head with an intact ligamentum teres was found in the acetabular cavity. The neck was completely eroded and the end of each fragment was bordered by a thin cortex of new bone which was covered by a thin fibrous layer from which sprang adhesions running to the capsule at its upper limit.

Macroscopic Appearance of the Excised Head.—The articular cartilage appeared whitish, clear and shiny without any irregularity, except at the fovea, where a small tag of fibrous tissue, presumably a part of the round ligament, was found attached (fig. 20). There was a slight thinning of the superior surface of the cartilage over an area 2 cm. in diameter. The underlying spongiosa was distinctly visible through this thin, bluish articular cartilage.

The specimen cut easily and was abnormally soft, except at the eroded neck surface, where it had normal bony resistance (fig. 21). The cut surface revealed an articular cartilage that varied from 0.5 to 5 mm. in thickness. Throughout

Fig. 19 (case 6).—Roentgenogram of the hip showing a diffuse reduction in density of the head with large circumscribed and markedly rarefied areas scattered in it.

the whole circumference, the articular cartilage was intact and adherent to the underlying narrow strip of subchondral bone. In the outer portion of the spongiosa corresponding to the areas of markedly reduced density in the roentgenogram were areas made up of brownish, broken-down fatty tissue of putty-like consistency. Embedded in these areas were small, fine fragments of bone.

Microscopic Appearance.—The articular cartilage as a whole was intact, although slightly thinned over the superior surface (fig. 22). Only a few of the cartilage cells were missing, and in their lacunae, small, dark bodies remains of the cartilage cells, were still seen. More normal cartilage cells were

encountered around the fovea. The thinning of the articular cartilage in the superior portion of the head appeared to be due partly to replacement of the superficial layer by the pericondral fibrous tissue, and to a greater extent to the invasion of the articular cartilage from the subchondral fatty marrow and vascular spaces, with the formation of huge and well defined cavities in it. These spaces contained fat, blood vessels and a few multinucleated giant cells; and were

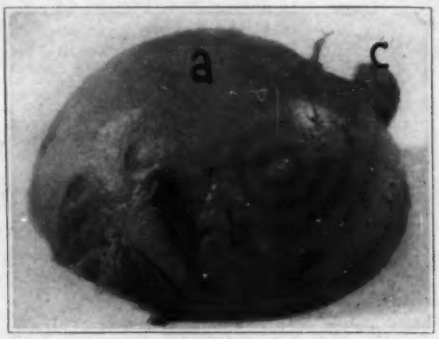


Fig. 20 (case 6).—Appearance of the femoral head showing smooth, whitish articular cartilage (*a*), thin, bluish cartilage (*b*) and ligamentum teres (*c*).

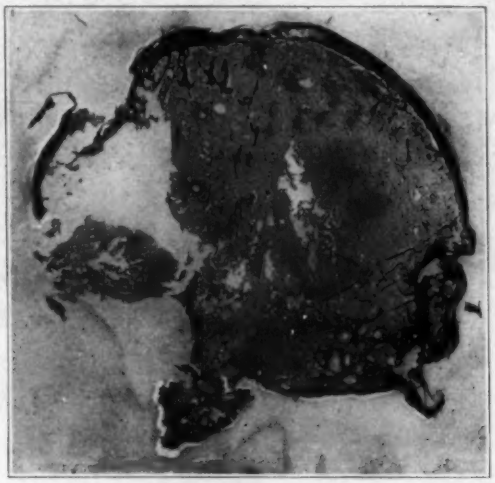


Fig. 21 (case 5).—Photomicrograph of a section of the femoral head showing marked loss of the bony trabeculae and absorption in articular cartilage.

partially lined by narrow strips of newly formed bone. Islands of newly formed hyaline cartilage were seen about these chondral marrow cavities (fig. 23). They appeared to arise from the deeper layer of the perichondrium and surmounted the newly formed lamellar bone in places. The cartilage cells were found singly or in twos enclosed by a capsule and separated by a bluish homogeneous matrix. As a whole, the thin layer of subchondral bone at the osteochondral margin was

preserved and appeared normal, so that, though markedly thinned out, the articular cartilage remained intact and attached to the spongiosa. At the fovea, remnants of the round ligament with a few slightly dilated blood vessels were seen. A small amount of osteoid tissue was laid down about some of the bony trabeculae near the vessels in this region. The brownish, granular material that nearly filled the spongiosa was made up of fat, poorly cellular marrow infiltrated with thin-walled blood vessels and a few monocytes. Embedded in this marrow were occasional small fragments of bony lamellae which showed well staining nuclei. This evidently was the picture of high grade atrophy.

Summary.—Summarizing the case, one finds:

1. Four years old intracapsular fracture of the neck of the femur with erosion of the neck fragments.

2. Roentgenogram showing marked diffuse decrease in density of the head as well as of the pelvis and shaft.

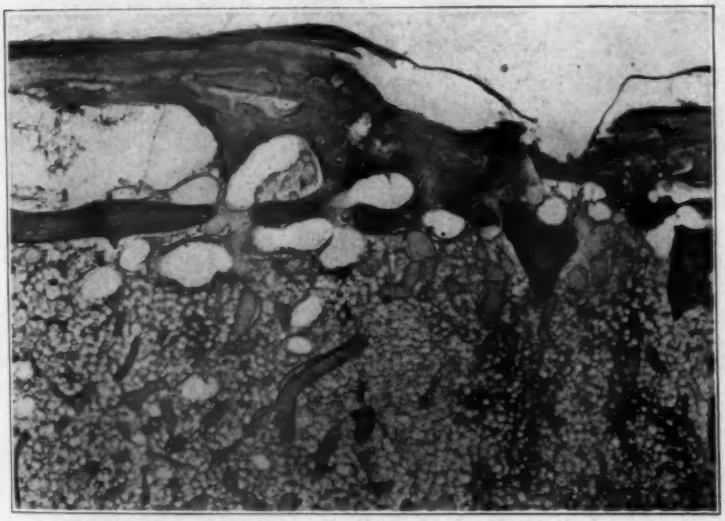


Fig. 22 (case 6).—Section of the superior portion of the articular cartilage invaded by the subchondral marrow and vascular spaces; × 60.

3. Living but markedly atrophied head with slight formation of osteoid tissue about the fovea.

4. Presence of the ligamentum teres containing blood vessels.

5. Marked thinning of the superior portion of the articular cartilage due partly to replacement by perichondral fibrous tissue and partly to invasion by the subchondral marrow and vascular spaces.

6. Formation of islands of new hyaline cartilage and lamellar bone in place of the old articular cartilage.

CASE 7 (PARTIALLY NECROTIC HEAD)

Case 7 is cited to show that a part of the head may remain alive and that the weight bearing portion of surviving articular cartilage of a

severely atrophic femoral head may be so thinned out by invasion and replacement from the subchondral fatty marrow that actual honeycombing of the articular cartilage occurs. The area becomes filled with marrow tissue in which strips of lamellar bone surmounted by new articular cartilage is later formed.

A woman, 52 years of age, three years before examination fell on her left hip and felt something give way. On attempting to rise, she found the left lower

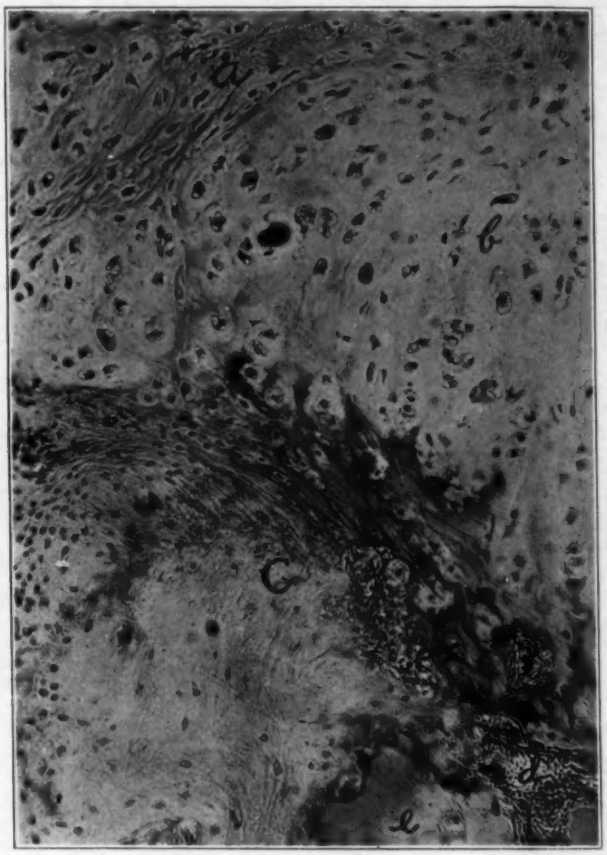


Fig. 23 (case 6).—Section of newly formed surface showing perichondrium (*a*), newly formed hyaline cartilage (*b*), new lamellar bone (*c*), vascular spaces (*d*) and remnant of the calcified portion of the old articular cartilage (*e*). Reduced from a magnification of × 160.

limb useless and markedly painful. She was told that she had a fracture of the neck of the left femur and was taken to a hospital, where the leg was immobilized and traction applied for five weeks. At the end of this period, she was allowed to go about with crutches, although she could hardly bear weight on the hip on account of pain. A roentgenogram of the left hip taken on the day of examination

revealed an old ununited intracapsular fracture of the neck of the left femur with separation of the fragments and absorption and erosion of the neck (fig. 24). The head, which was found to be in the acetabulum, showed a marked diffuse decrease in density, except for a small region in its superior portion, which revealed almost no reduction in density. There was an irregular area of increased density in the central portion of the infratrochanteric portion of the shaft, the cause of which was not known.

A Whitman reconstruction operation was performed three days after the examination. At operation, the neck fragments were found eroded away and the greater trochanter displaced upward to the level of the superior acetabular margin. The head was markedly adherent to the acetabulum by means of thick fibrous tissue which was attached to the fracture surface. In removing the head, the fibrous adhesions and the ligamentum teres, which could hardly be identified, had to be cut.

Macroscopic Appearance of the Excised Head.—The femoral head showed an almost normal spherical shape, except for a large depression at the superior

Fig. 24 (case 7).—Roentgenogram of the hips. Note the markedly diffuse decrease in density of the head of the left femur with a small dense area at its superior portion and the calcification at the upper third of the femoral shaft.

surface about the fovea (fig. 25*A*). This depression was due to a loss of the articular cartilage and of the underlying spongiosa. It measured 2.5 cm. in diameter and 1.5 cm. in depth. A mass of fat with a few minute pieces of bone lying loosely in it was seen occupying this region. The articular cartilage about the defect was thin. It was made up of irregular and discrete areas of glistening, bluish cartilage, which extended to the outer circumference of the head, where they merged into the clear, whistish, shiny articular cartilage. There was a dense unchanged island of bone 1 by 0.5 cm. along the superior articular surface as shown in figure 25*B*. The fracture surface of the head showed a layer of thick fibrous tissue, which was adherent to it, while that of the lower fragment was covered by dark red, granular tissue in which small fragments of loose bone were embedded.

On being sawed, the head was found abnormally soft in places which cut with marked ease. The cut surface presented an articular cartilage that varied in thickness from 0.5 to 4 mm., and it also showed the erosion in the articular cartilage at the superior surface of the head. The center of the spongiosa was occupied by

fat in which lay small pieces of bone. Only about the fracture surface and at the osteochondral junctions did the masses of fat merge into the fine, fibrillary, whitish spongiosa, which appeared normal. Ordinary hematoxylin and eosin stains were made, as well as the scharlach R stain for fat.

Microscopic Appearance.—As a whole, the head was alive and presented a picture of severe atrophy. In spite of marked thinning, the articular cartilage was continuous and adherent to the underlying narrow strip of subchondral bone, except at the superior portion about the fovea, where the head showed a marked loss of substance in both articular cartilage and spongiosa. In general, the cartilage cells were present and well stained. The articular cartilage about one of the osteochondral junctions had been completely replaced by fibrocartilage. Slight calcifications of the deeper layer of the rest of the articular cartilage could be noted. As in the other femoral heads that remained alive but became atrophic after the fracture, there was an outstanding change in the articular cartilage, which was present in a greater degree. This change started at the superior

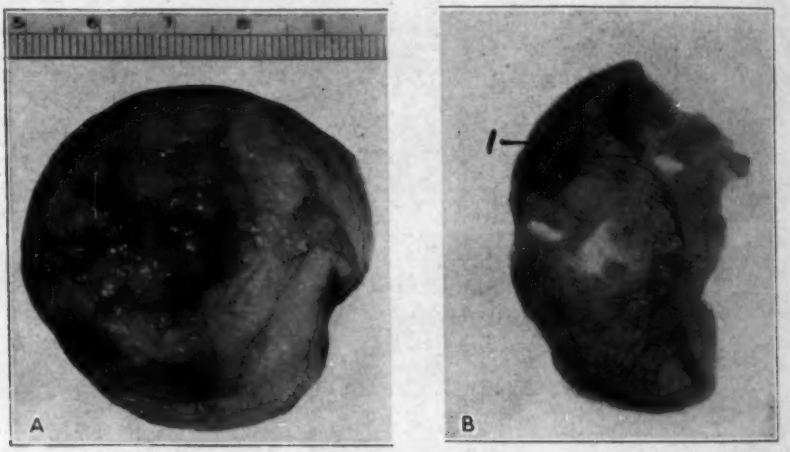


Fig. 25 (case 7).—*A*, photograph of the excised head, and *B*, roentgenogram of a slice of the head showing atrophic living portion and small dense necrotic portion along superior articular cortex (1).

portion of the articular cartilage which was in contact with the acetabulum, and consisted in an invasion by the subchondral fatty marrow and vascular spaces, which resulted in the formation of marrow cavities in the cartilage layer (fig. 26). With the progress of the atrophy as in this case, and the subsequent dilatation of the subchondral marrow cavities, there was also a corresponding enlargement of these chondral marrow spaces. The cavities contained fat, a few red blood cells, monocytes, osteoblasts and occasional multinucleated giant cells. The process extended from the superior portion of the articular cartilage down and along the outer circumference of the head, replacing and dissecting the cartilage as it advanced into distinct and fairly separated layers. Along the margins of these intrachondral spaces, strips of newly formed lamellar bone were seen. The part of this layer of new bone which overlay these spaces spread out simultaneously with the enlargement of the latter, and assumed the general appearance of subchondral bone. In places, small newly formed bony projections which were parts of the marginal lamellar bone of the chondral marrow cavities, were seen as if budding off

from the newly formed subchondral bone. Embedded in a matrix of fatty marrow and projecting down from the subchondral bone, these parts of the marginal bony lamellae became new bony trabeculae. The superficial layer of the old and split articular cartilage soon disappeared and became replaced by a more or less dense fibrous tissue which was slightly vascular, and which subsequently overlay the newly formed subchondral bone. Along their junction, distinct calcification of the deeper layer of the fibrous tissue was noted. In this region, the fibrous tissue assumed an embryonal appearance and, in places, gave rise to islands of newly formed cartilage

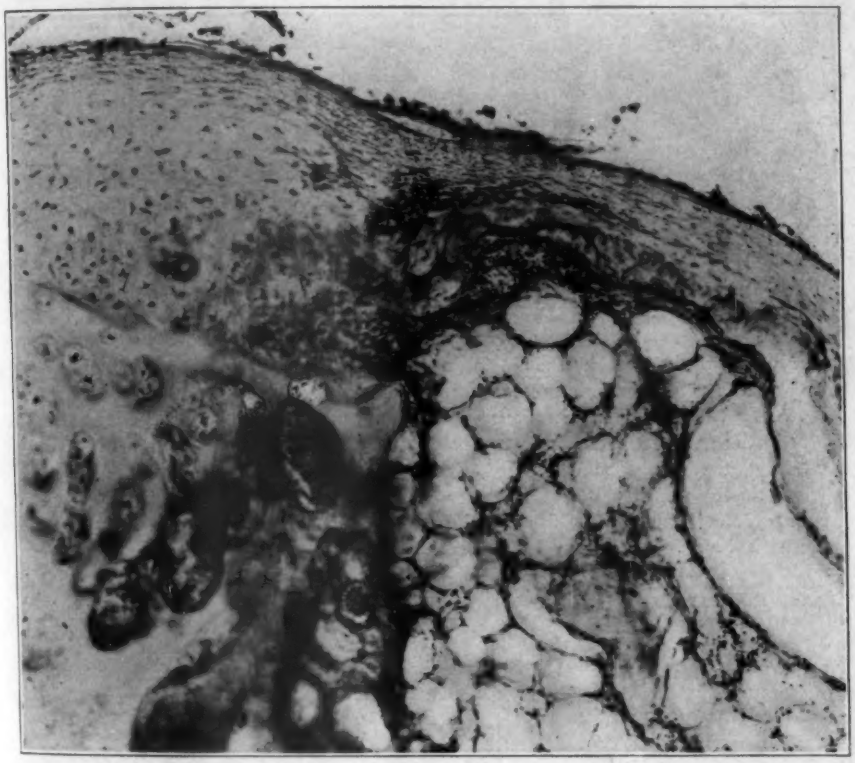


Fig. 26 (case 7).—Section of the superior portion of the articular cartilage showing invasion by the subchondral marrow and vascular spaces with replacement of the old cartilage and formation of new cartilage and lamellar bone. Reduced from a magnification of × 160.

cells lying in a bluish, homogeneous matrix. These islands of new cartilage cells occupied the sites of the thin, bluish cartilage nodules about the erosion as seen in the gross specimen. It was therefore evident that throughout this area an active reparative process was taking place. And this consisted in the formation of a new layer of articular cartilage with a slightly calcified deeper portion, surmounting newly formed subchondral bone and spongiosa in the region of the old articular cartilage. This histologic appearance makes it likely that a refilling and disappearance of the erosion in an atrophic head occurs by a complete reformation.

sooner or later, of the cartilaginous and osseous elements of the femoral head. This is well illustrated by the case reported by Heine, as will be briefly described later.

The spongy portion of the head was made up of markedly dilated marrow spaces filled with fat, a few blood vessels and occasional monocytes. Its bony trabeculae everywhere showed well staining bone cells. The dense island along the superior articular cortex consisted of necrotic bone with its original trabeculae and bony cortex unaltered. It was bordered by fibrous tissue along its deep surface which was producing slight absorption of the dead trabeculae. Along the cortex it was surmounted by a necrotic and markedly calcified articular cartilage which showed superficial erosion and replacement by fibrous tissue. This small area presented a picture of necrosis without substitution as contrasted with the marked atrophy which the living portion of the head had undergone. At the center of the living portion the trabeculae were represented only by a few small detached fragments of living bone. At the osteochondral junctions and along the fracture surface, however, the bony lamellae showed a slight increase in size and number. A thick layer of fibrous tissue was found attached to the eroded fracture surface of the head, and a cortex of newly formed bone surrounded by osteoblasts and slightly fibrous and vascular marrow was seen along its whole extent. One must consider the possibility of complete necrosis of the head with creeping substitution of all except the dense area in the upper portion, but partial necrosis seems the more plausible explanation.

The distal fragment, the upper spur of which was clipped off, also showed a picture of marked erosion, necrosis and absorption. The cancellous spaces, especially those about the fracture surface, were hugely dilated and contained slightly loose and vascular connective tissue which was infiltrated with fat, degenerated red blood cells and occasional small and necrotic fragments of bone. On being traced laterally, the spaces soon showed rich collections of multinucleated giant cells (osteoclasts) which had markedly absorbed and reduced the necrotic cortex to a thin layer of bone. No evidence of new bone formation was seen. Further down the neck, however, a few well staining bone cells could still be discerned about the haversian canals, thus giving a picture of partial necrosis as seen in areas with diminished blood supply.

Summary.—The case may be briefly summarized:

1. Three years old intracapsular fracture of the neck of the femur with erosion and separation of the neck fragments.
2. Roentgenograms showing a marked decrease in density of the fragments with absorption and erosion of the neck.
3. Largely living and severely atrophic femoral head with a necrotic area of bone and cartilage at the superior portion.
4. Presence of the ligamentum teres and of adhesions to the eroded neck surface.
5. Invasion of the articular cartilage by the subchondral fatty marrow with erosion and loss of substance of the head at its superior portion.
6. Active formation of new articular cartilage and bone about the site of the erosion.
7. Necrosis with active absorptive process in the femoral neck.

COMMENT ON CASES IN WHICH HEAD FRAGMENT REMAINED ALIVE

It is clear from cases 5, 6 and 7 that, after a femoral head has been separated from the distal fragment following an intracapsular fracture of the neck of the femur, it may still be preserved and its vitality maintained by adequate nutrition from the vessels of the round ligament.

This was further unequivocally shown in the recent studies and investigations of Frangenheim,[6] Schmorl [4] and Hesse.[15] Schmorl, for instance, found that in only one of thirty-four such cases was there a total necrosis of the femoral head. He cited a case in a young man in which, in spite of the complete destruction of the capsule around the femoral neck, the whole head was sufficiently nourished by the vessels of the ligamentum teres to prevent necrosis. Even in old age, these vessels may continue to supply the femoral head adequately. Nussbaum showed this in a person 64 years of age. Here he also found an extensive anastomosis between the arteries of the ligamentum teres and those of the femoral neck. Frangenheim showed, in a man 85 years of age, large vessels in the round ligament which furnished sufficient nourishment to preserve the femoral head.

From the descriptions of the specimens (cases 5, 6 and 7), it may be noted that the head, except in case 7, in which a small necrotic area was present, had remained alive, as shown by the presence of living cartilage cells in the articular cartilage and normal-staining bone cells in all the lamellar systems of the spongiosa. This fact more than suggests the presence of sufficient circulation and nutrition from the blood vessels of the ligamentum teres. But, owing to the separation of the fragments and subsequent throwing of the head out of function, the latter undergoes an atrophic change, which consists of a diminution in the number and size of the bony trabeculae, and a dilatation of the marrow cavities which become filled with fatty marrow. The degree of atrophic change bears a direct relation to the duration of the functional loss. As a rule, traumatic influence on such living structures is not as readily productive of damage as in a necrotic head. This, in part, explains the absence of gross erosions of the cartilage and bone in the first two cases. Such erosions are altogether absent in a less atrophic head, as in early cases. Even early in the process, certain histologic changes involving the articular cartilage and starting at its superior portion where the femoral head is in contact with the acetabular wall can be well recognized. These consist in an invasion of the deeper layer of the cartilage by the subchondral fatty marrow and vascular spaces, presenting a picture of marrow cavities in the cartilage layer. These medullary spaces contain fatty and slightly fibrous marrow, mixed with lymphoid structures, red blood cells, osteoblasts and a few large multinucleated giant cells, which are seen to proceed from the subchondral region. A similar process is frequently encountered at the osteochondral junction, but for which no definite explanation has been given judging from the prevailing and conflicting views. Importance has been attached to this process by Pommer,[16] who thought it

16. Pommer, G.: Zur Kenntnis der Ausheilungsbefunde bei Arthritis deformans besonders im Bereich ihrer Knorpelusuren nebst einem Beitrag zur Lacunären Knorpelresorption, Virchows Arch. f. path. Anat. **219**:261, 1915.

to be a characteristic change in the early stage of genuine arthritis deformans. Recently, however, after an examination of 15,000 joints, Heine [17] came to the conclusion that it is not specific for arthritis deformans, as it is also commonly seen in physiologic resorptive processes.

It must be admitted that such a process in the articular cartilage accompanies atrophy of the head, and this naturally raises the question whether, like the bone, cartilage with its secondary invasion by the subchondral vascular spaces may also undergo atrophy following disuse of the part. Such an association is so constant and striking that a study is being made as to its real significance. It may be looked on as both an absorptive and a formative change of the articular cartilage which is associated with, and perhaps caused by, the atrophy. Although ordinarily trauma to a living but atrophic femoral head is not productive of damage; nevertheless, where this atrophic change has advanced to a marked degree and the replacement of the articular cartilage by the subchondral marrow is extensive, slight injury, as the constant pressure against the acetabulum, may cause destruction or indentation of the remaining, thin articular cartilage at the superior surface of the head. Such a secondary absorptive change in the head occurring mainly at the point of contact bears a certain similarity to the not infrequent pressure atrophy. Kaufmann [18] stated that under the influence of continuous pressure, even from a soft and elastic substance, increased resorption of bone both lacunar and smooth, occurs with resulting atrophy. As an example may be mentioned the erosion of bone by aneurysms, particularly those of the aorta, with disappearance of portions of the vertebrae, the ribs and the sternum.

The origin of the multinucleated giant cells and the rôle they assume in atrophy are still disputed questions. Pommer [19] thought that they were derived from the endothelial cells of the blood vessels. With the slowing of the blood flow and the rise of blood pressure because of the lack of functional demand on the circulation, injury of the vessel walls from insufficient nutrition occurs which results subsequently in the formation of osteoclasts. It may also be assumed that owing to generalized atrophy the bone building cells become atrophic and consequently their functional capacity becomes reduced. This atrophy then leads to a decrease in osteoblastic activity, and hence the normal relation between bone formation and absorption is disturbed. As a result of this insuffi-

17. Heine, I.: Ueber primäre chronische Gelenkerkrankungen, Ztschr. f. orthop. Chir. **49**:7, 1928.

18. Kaufmann, E.: Spezielle pathologische Anatomie, Berlin, G. Reimer, 1896, vol. 1, p. 830.

19. Pommer, G.: Ueber Osteoporose, ihren Ursprung und ihre differentialdiagnostische Bedeutung, Arch. f. klin. Chir. **136**:1, 1925.

ciency of the osteoblasts and the presence of the multinucleated giant cells, replacement and absorption of the cartilage and bone occur. Although the accuracy of this explanation is obviously open to criticism, nevertheless the histologic appearances more than suggest that the invasion with subsequent replacement of the articular cartilage by the subchondral marrow is partly due to phagocytic activity.

With the advance of the atrophic process in the spongiosa, a simultaneous and progressive dilatation of these chondral cavities and perhaps increased activity of the phagocytes appear at the expense of the cartilage. The remaining articular cartilage overlying these marrow spaces may be reduced to a sheet so thin that actual breaks may be encountered (case 6) or definite erosions of the cartilage with replacement by honeycomb-like fatty marrow spaces and subsequent formation of new articular cartilage may be seen (case 7). If the atrophy advances even further, numerous new lamellae of bone having a new cartilaginous articular surface replacing the whole of the old articular surface of the head may be encountered. This is seen to start at the portion of articular cartilage which is in contact with the acetabulum and later extends along the outer circumference of the head (case 7) and leads to a complete reformation of its articular surface. A case reported by Heine [20] is cited to serve as illustration.

The patient was a woman, 46 years of age, who sustained a complete intracapsular fracture of the neck of the right femur with a resulting pseudo-orthosis for five years. A roentgenogram of the right hip showed separation of the fragments and a considerable diffuse decrease in the density of the head of the femur. At autopsy, the head was found adherent to the acetabulum by the ligamentum teres with thick fibrous tissue attached to the fracture surface. On microscopic examination, the entire head was found well preserved in spite of the severe atrophy. There was good staining of the cell nuclei everywhere, and no signs of necrosis could be detected. In the region of contact between the head and the acetabulum, an entirely new articular surface had formed on both sides. A new layer of bone having a new cartilage covering was found over the old articular cartilage about the region of the fovea. Here, the old articular cartilage had completely disappeared in some areas and in its place a layer of newly formed lamellar bone was seen. The old articular cartilage near the fovea was honeycombed by dilated medullary cavities which showed intervening narrow walls of bluish-white hyaline cartilage. These medullary spaces were filled in part by fatty marrow and in part by a fibrous and lymphoid tissue which contained a number of multinucleated giant cells. The cells of the old articular cartilage at the outer circumference of the head showed marked proliferation.

Although secondary degenerative change in a separated and necrotic femoral head is the rule, nevertheless in a separated head that remains alive following the fracture, no such permanent change occurs. The

20. Heine, I.: Zur Kenntnis der Hüftgelenkveränderungen bei veralteten subkapitalen Schenkelhalsfrakturen, Zentralbl. f. Chir. **51**:1390, 1924.

only change that occurs in the articular cartilage of the living head is the encroachment on it of the subchondral fatty marrow. A physiologic resorptive process commonly seen even in normal joints, it invariably disappears rather promptly or readily leads to a reformation of the articular surface. Its disappearance is especially hastened on resumption of function of the part, and this is particularly true in the early cases in which no gross erosion of the articular cartilage has as yet taken place. If, however, the atrophy of the head has advanced to a marked degree, as in cases of more than three years' duration, with actual erosion and with complete disappearance of the articular cartilage and underlying spongiosa over its superior portion, a simultaneous formation of new articular cartilage and subchondral bone may result, with complete replacement of the old articular cartilage of the head. Unlike the secondary degenerative, absorptive and progressive change in a necrotic head, therefore, this change in a living head is transitory and reparative and ends in the formation of new articular cartilage and bony trabeculae.

There are also roentgenologic observations which are important, but which have received no attention. If the roentgenogram, however, is considered together with the pathologic changes taking place in the femoral head and neck, they will be found to agree. Except in early cases, in which tissue changes in either the head or neck have not as yet occurred, the roentgenogram is of great significance in determining the nutritional state of the head and neck of the femur. The basic facts underlying the roentgenologic interpretation are as follows: decrease in the density of a varying degree is always noted in the heads that remain alive but which become atrophic after the fracture. A head, however, that becomes necrotic following the fracture, retains its normal density for a considerable time afterward. When the necrotic head is subsequently revascularized, this is shown by a corresponding decrease and irregularity in density. New bone formation in the secondarily vascularized regions is indicated by irregular, fine densities scattered in these areas. A necrotic head that is secondarily vascularized may after a long time show as much reduction of density as an atrophic living head. But the former may usually be distinguished from the latter by its patchy appearance and simultaneous marked absorption and distortion of normal contour.

REUNION OF THE FRAGMENTS

When the fragments after a complete intracapsular fracture of the neck of the femur remain in good apposition or are impacted, the head whether alive or necrotic, may unite with the distal fragment. A fibrous or bony consolidation may follow, depending on the duration of the apposition of the fracture surfaces.

CASE 8 (NECROTIC HEAD)

A case of twenty-four days' duration may be cited to indicate a necrotic head entering into fibrous union with the distal fragment. A beginning erosion with fibrous tissue replacement of the articular cartilage about the fovea was also noted. Although the ligamentum teres was present there was no sign of newly formed vessels or connective tissue invading the head from it.

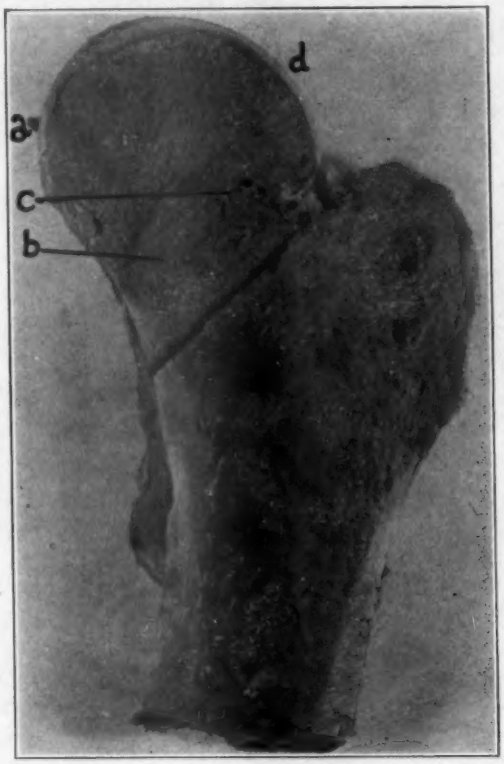


Fig. 27 (case 8).—Cut surface of the upper third of the femur removed at necropsy showing ligamentum teres (*a*), fracture line (*b*), area of impaction (*c*) and necrotic but intact articular cartilage (*d*).

The patient was a man 80 years of age. He slipped and fell on his left hip which resulted in disability. He was immediately taken to a hospital. A roentgenogram taken the next day showed an impacted intracapsular fracture of the neck of the left femur. He was put to bed, where he remained until his death, twenty-four days after the injury. The upper third of the femur was removed at autopsy.

Macroscopic Appearance of the Specimen.—The fresh cut surface of the specimen showed a transverse fracture of the proximal third of the neck of the femur with impaction of the fragments in the lateral third of the fracture line (fig. 27). The periosteum of the neck was intact on the mesial side. A portion of

the ligamentum teres was attached to the head. The articular cartilage was smooth, clear and intact, except at the region of the fovea, where it was slightly eroded. At about the center of the head there was a darkly stained oval area which extended down into the neck across the fracture line to the distal fragment. The rest of the interior of the head was yellowish and uniformly trabeculated. There was slight mobility between the fragments.

Microscopic Appearance.—The round ligament was represented by a narrow strip of slightly dense avascular connective tissue which did not penetrate the spongiosa. The articular cartilage about this region was very slightly eroded and replaced by fibrous tissue which extended from the region of attachment of the ligamentum teres to the head (fig. 28). Except for this erosion, the articular cartilage as a whole, although necrotic, was intact and adherent to the underlying subchondral bone. Most of the cartilage spaces, especially around the fovea, were empty. The remaining cartilage cells stained rather poorly. There was marked calcification of the deeper layer of the articular cartilage. The bony lamellae were

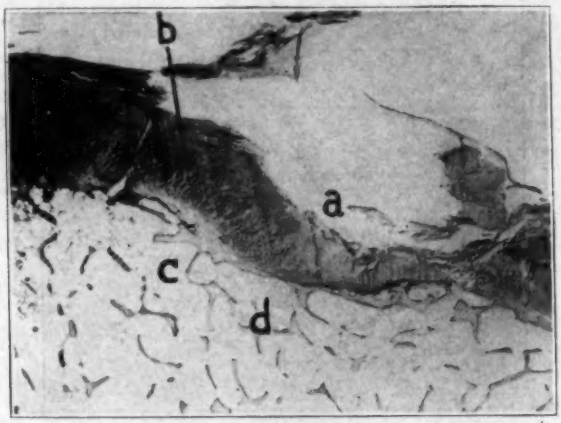


Fig. 28 (case 8).—Section of the fovea showing the absence of vascularization of the spongiosa from the ligamentum teres; × 60.

necrotic and lay except in the dark area in a matrix of degenerated marrow, which was practically acellular and avascular and contained large empty spaces. No attempt at replacement of these necrotic bony lamellae by fibrous connective tissue was seen. However, in the oval area extending for a distance of 2 cm. from the fracture line up into the neck and base of the head, and in the region of contact between the fragments, active absorptive and regenerative changes were encountered. Here the necrotic bony trabeculae of the head were embedded in a highly vascularized connective tissue rich in blood vessels, red blood cells, and containing a few osteoblasts and multinucleated giant cells. At the borders of some of these necrotic bony lamellae newly formed bone surrounded by numerous osteoblasts was seen. Active lacunar absorption of bone was taking place in the same region. The vascularized tissue bridging the fracture line appeared to proceed from the marrow of the living distal fragment. The region of impaction was filled with small fragments of dead bone.

As in an ununited intracapsular fracture of the neck of the femur, the neck portion of the distal fragment presented a striking picture of slight formative and simultaneously active absorptive processes. Throughout the region of contact

between the fragments, a broad band of highly vascular connective tissue was seen extending from the cancellous spaces of the neck into the head. In this region, a network of small newly formed bone surrounded by osteoblasts was seen about the fracture surfaces (fig. 29). At the periphery of the neck, however, a picture of partial necrosis of the bony lamellae was encountered. Here, the bone cells were found only about the haversian canals and were absent in the compact portion of the bone and the intermediate lamellae (fig. 30). An active lacumar absorption of these partially necrotic bony lamellae was also taking place.

Fig. 29 (case 8).—Photomicrograph of section showing the region of contact of the fragments: original bony lamella of the distal fragment (*a*), fracture line (*b*), proximal fragment (*c*), rich network of newly formed bone (*d*) and osteoblasts (*e*). Reduced from a magnification of × 160.

Summary.—The case may be summarized as follows:

1. Impacted intracapsular fracture of the femoral neck of twenty-four days' duration with total necrosis of the head and partial necrosis of the neck.

2. Presence of the ligamentum teres, but no signs of revascularization of the head from it.

3. Beginning erosion of the articular cartilage about the fovea with fibrous tissue replacement.

4. Slight replacement of the necrotic bony lamellae and formation of new bone in the head at the region of contact with the distal fragment.

5. Extension of vascular connective tissue from the distal fragment across the fracture line into an adjacent portion of neck and head. No sign of vascularization of the necrotic head through the intact periosteum along mesial side of fracture.

Fig. 30 (case 8).—Periphery of the distal portion of the neck showing necrosis and marked lacunar absorption of the bony trabecula with slight formation of new bone. Reduced from a magnification of × 160.

6. Partial necrosis, slight formation of new bone and active bone absorption in the distal fragment of the neck near the fracture line.

Comment.—Here one has an early case of intracapsular fracture of the neck of the femur in which the fragments are in good apposition. It may be noted that in this case there was no attempt at revascular-

ization of the necrotic head from the region of the ligamentum teres. The beginning stage of bony consolidation which mainly proceeded from the partially necrotic neck was seen. With this there were also early signs of organization of the necrotic head in its secondarily vascularized region.

CASE 9 (NECROTIC HEAD)

If a necrotic head such as that described in case 8 is allowed sufficient time in good apposition with the distal fragment, a complete osseous consolidation may result. Case 9 is cited to indicate this bony union.

The patient was a woman 49 years of age. One day before examination, she fell on her left hip, and because of the subsequent pain and disability in it, she had to be carried to her bed. Roentgen examination of the hip on the same day showed an intracapsular fracture of the neck of the femur with separation of the fragments. On the next day, a bone pegging operation, using a beefbone peg, was performed. The ligamentum teres was not identified. The cavity of the joint was found filled with bloody fluid. The patient was placed in a long plaster of paris spica, in which she remained for nearly three months. The cast was then removed, and passive movement of the leg was instituted. She was then allowed to be up and about with the aid of crutches. The roentgenogram of the hip taken nearly four months after the operation showed bony healing of the fracture (fig. 31 *A*).

Eight months after the operation, the patient began to have pain in the left hip. Roentgen examination at this time showed an almost normal density of the head, as is regularly seen in a necrotic head, and slight irregularity of its weight bearing portion (fig. 31 *B*). The neck revealed a slight diffuse decrease in density. The bone peg did not show any change. Because of the persistent pain in the left hip, an operation was performed four months later for the removal of the bone peg. At this operation, the fracture was found to be solidly healed. The patient subsequently passed an uneventful convalescence and went on to recovery with almost perfect use of her left leg until a year after the second operation (nearly two years after the bone pegging operation); then she started to complain again of pain and disability of the same hip (fig. 31 *C*). A roentgenogram taken at this time showed absorption and collapse of the femoral head with separation of a portion of it at its weight bearing portion. Another operation was done for the removal of the collapsed portion of the head. This was found almost free in the joint, and on histologic examination it was seen to be made up of necrotic, although intact, articular cartilage and necrotic, unreplaced bony lamellae, which were embedded in a matrix of degenerated marrow.

It is of great interest to note that the portion of the peg about 4 cm. long lying in the trochanteric region of the distal fragment was markedly eroded and thinned and had a moth-eaten appearance, while the part included in the neck, 2 cm. long, was put slightly eroded (fig. 32). The whole portion of the peg in the head, however, remained unchanged. This might be explained by assuming that a gradation of vascularization and vitality of the fragments after complete intracapsular fracture of the neck of the femur exists. Because of the absence of the ligamentum teres and its vessels, necrosis, loss in vitality and failure in revascularization of the head occur after the fracture, which accounts for the unchanged condition of the part of the peg in this region. In a similar manner, and following

the complete fracture, there results a destruction of the vessels along the neck, which are known to be the main source of nutrition for the femoral neck. Consequently, a diminution in vascularization and vitality with subsequent partial necrosis, especially marked along the margins, as observed in histologic sections,

Fig. 31 (case 9).—*A*, roentgenogram of the left hip taken four months after the bone pegging operation, showing healing of the fracture and practically no reduction in density of the femoral head. *B*, roentgenogram of the hip taken a year after the operation showing the dense head with beginning collapse of its weight bearing portion. *C*, roentgenogram taken two years and two months after the bone pegging operation. Note the separation of the collapsed and markedly dense portion of the head.

appears in it. The slight absorptive change at the corresponding part of the peg can well be explained by this condition of the neck. On the other hand, as the intertrochanteric region is supplied not only by the vessels running along the femoral neck, but also by a branch of the superior nutrient artery, the destruction of the neck vessels alone would result in little or no impairment of nutrition of this region. This accounts for the more or less normal vascularization and vitality of the trochanteric region of the distal fragment, as shown by the marked absorption and erosion of the peg included in it.

Summary.—Summarizing the significant features, one has:

1. Bone pegging operation performed one day after the injury, followed in four months by bony healing of the fracture.

2. Necrotic head eight months after the operation, as shown by its normal density in the roentgenogram.

3. Secondary collapse of the weight bearing portion of the head almost two years after the healing of the fracture.

4. Eroded appearance of the bone peg within the tronchanteric region, slight erosion of the part included in the neck and unchanged condition of the peg lying in the head.

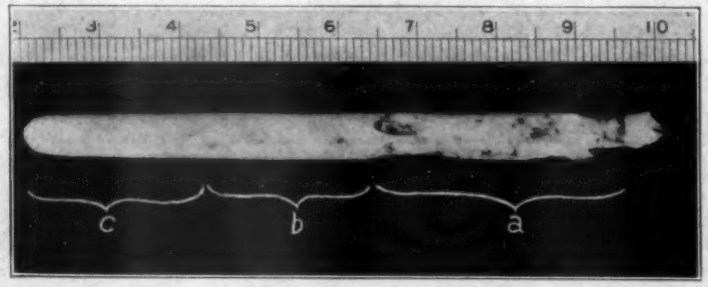


Fig. 32 (case 9).—Appearance of the removed bone peg showing portion included in the trochanteric region of the femoral shaft (*a*), part in the neck (*b*) and portion in the head (*c*).

5. Necrotic head, as evidenced by the roentgenogram, by the absence of the ligamentum teres and by the appearance of the peg.

6. A slight absorption of the neck.

Comment.—On the basis of the roentgenologic observations in separated femoral heads after fracture of the neck this femoral head can be considered with a high degree of certainty to have been necrotic. This is indicated by its diffuse normal density as seen in the roentgenogram made long after the bony union of the fracture took place. With this change in the head, it may be assumed that there were also varying degrees of necrosis with subsequent reduced vitality of the neck in this case, as suggested by the appearance of the bone peg included in it, by the diffuse rarefaction and erosion of the neck as seen in the roentgenograms and indirectly by the uniform histopathologic observation of necrosis (partial or com-

plete) in other femoral necks following such fracture. But in spite of the total necrosis of the head and the varying degrees of necrosis of the neck, bony healing of the fracture, although delayed, occurred within four months after the bone pegging operation. The collapse of the weight bearing portion of the head, which became evident two years after the bony union of the fracture, suggests that an efficient secondary vascularization of the necrotic head from the distal fragment, with complete organization and transformation had not appeared. Consequently, secondary degenerative change in the form of collapse, especially of the weight bearing portion of the head, took place. It is therefore justifiable to assume that healing of the fracture is possible from the slow ingrowth of callus from the necrotic and eroded neck. Although directly accountable for the healing of the fracture, the revasculization of the necrotic head from the distal fragment is a rather slow and weak process which invariably fails in thoroughly organizing and transforming it. As a consequence, the head remains necrotic and as in the case in which there is a necrotic and separated femoral head, it undergoes a secondary degenerative change. In this connection, and to show further the possibility of bony union of the fracture when the head is necrotic, a case reported by Axhausen [13] may be mentioned.

This occurred in a schoolboy, 16 years of age, who, ten months before examination, fell on his right hip. In spite of slight soreness in the hip, he was able to walk home with practically no disability. A roentgenogram taken at the time of the injury showed an impacted intracapsular fracture of the neck of the femur. The fracture healed, and the youth became able to make use of the limb without the least discomfort. Then, a few weeks before examination, he began to have pain and disability in the hip. The roentgenogram taken at the time of examination showed evidence of bony union, but with secondary collapse of the femoral head. The head, which was resected later, retained its normal density, as do other necrotic femoral heads. On microscopic examination, it was found to be totally necrotic, with replacement of the marrow at the upper osteochondral margin by a highly vascularized connective tissue which apparently extended from the distal fragment. The necrotic bony lamellae in this region showed lacunar absorption with simultaneous formation of new bone. This formation of new bone and reorganization were especially marked about the fracture surfaces and extended to the region of the epiphyseal cartilage. The articular cartilage was without nuclei. It was fissured and eroded for an area of 2.5 cm. in its superior portion exposing the underlying spongiosa.

CASE 10 (NECROTIC HEAD)

In the case of impacted intracapsular fracture of the neck of the femur now to be described, the roentgenograms showed that bony union occurred. But the proximal fragment was necrotic, as shown by the roentgenograms, and consequently it underwent a gradual disintegration and collapse in its weight bearing portion.

A man, aged 55, fell on his left hip, Aug. 8, 1925. On account of the resulting pain and disability in this hip, he was unable to walk and had to be carried

home on a stretcher. The roentgenogram taken three days later showed an impacted intracapsular fracture of the neck of the femur. The extremity was put up in a long plaster of paris spica, in which it remained for thirty-one days. Roentgenograms taken at this time showed bony union of the fracture. After six weeks he walked on crutches and after four months he discarded them. However, after six months the pain again became so severe that he resumed the use of crutches. A roentgenogram eight and a half months after injury showed slight collapse and irregularity in the weight bearing portion of the head and reduced density in the mesial portion of head fragment apparently from invasion of tissue from the distal fragment (fig. 33 *B*).

The patient was again placed in a plaster of paris spica three months later, and remained in this cast for several weeks. Since then there has been marked limitation of motion and adduction deformity of the hip and pain on walking has been so great that he has continued the use of crutches. Roentgenograms were taken twenty months, and three years and four months after the injury. They showed signs of a slowly progressive collapse of the weight bearing portion of the head and a progressive invasion and absorption of the rest of the head with replacement by irregularly arranged spongy bone. This is revealed in figure 33 *C* by the blotchy character of the shadow in the weight bearing portion and the reduced density in the lateral or nonweight bearing portion (*a*) projecting beyond the acetabular margin three years and four months after injury. It is evident that transformation was produced by tissue invasion from the distal fragment, but there appear to be no signs present by which one can say definitely that there was invasion from the round ligament. Figure 33 *C* also shows that a long time after union has occurred the density of the necrotic head which at first is unaltered may be as markedly reduced by invasion and transformation as is that of the living distal fragment and innominate bone by atrophy of disuse.

Case 10 shows that when the head becomes necrotic, bony union of the fracture may occur, but as a result of weight bearing the head may collapse and become markedly deformed before long transformation takes place, giving a poor functional result.

CASE 11 (NECROTIC HEAD)

In case 11, there was bony union in the presence of roentgen evidence of necrosis of the head fragments, but weight was not borne on the limb for eleven months and then only with the aid of canes for fourteen months. Transformation of the head was almost complete at the end of this time without collapse of the weight bearing portion and the hip was improving so that a fairly good functional result appeared to be in sight.

A man, aged 58, while boarding a street car, fell and forcibly struck his left hip on the step of the car. Because of pain and disability in the hip, he had to be aided to a stretcher, in which he was taken to the University of Chicago clinics. A roentgenogram showed complete intracapsular fracture of the neck of the femur with slight displacement of the fragments. With the patient under ethylene anesthesia, closed reduction was performed on the following day; and with the limbs abducted and internally rotated, a double, long plaster of paris spica was applied (fig. 34 *A*). The lower fragment was displaced laterally about 0.75 cm. The cast was removed after ten weeks and another roentgen examination of the hip was made. It showed that the fragments were in apposition but the lower frag-

ment was externally rotated. There was moderate reduction in density of the fragment ends where they came in contact and the lateral half of the head fragment showed reduced density for 0.5 cm. back from the fracture line. There was a spongy bony shadow across the fracture line. The rest of the head cast a shadow of the same density as that at the time of injury except in the region of

Fig. 33 (case 10).—*A*, roentgenogram of the left hip taken three days after the injury. *B*, roentgenogram taken eight and one-half months after the injury. Note the dense femoral head and collapse of its weight bearing portion. *C*, roentgenogram taken three years and four months after the occurrence of the fracture. Note the marked absorption of the head. The outer circumference of the head which was nonweight bearing (*a*), although showing marked reduction in density, maintains a fairly normal contour. This portion shows that a necrotic area when not subjected to stress may after a long period be transformed and reduced in density without changing form.

the fovea where there was an oval shadow of reduced density 1 cm. in its short diameter. The distal fragments and the innominate bone showed reduced density from atrophy of disuse. The interpretation is that the head became necrotic, that there was bony union of the fracture and that invasion and transformation of the dead head had begun, both from the round ligament and from the distal fragment across the healed fracture. The peroneus nerve was paralyzed and the limb

Fig. 34 (case 11).—*A*, roentgenogram taken four days after repositioning of the fragments, which was performed on the day of the injury. *B*, roentgenogram taken three months after the injury, showing normal density of the head except for slight rarefaction about the fovea and repair of the fracture. *C*, taken five and one-half months after injury, shows a large area of irregular absorption and replacement of the head about the fovea (a). *D*, taken eleven months after injury, shows about three fourths of the head transformed by invasion from both the fovea and from the distal fragment.

remained swollen for six months. The patient went on crutches for eleven months bearing no weight on the limb. Roentgenograms were taken four months, five and a half months, eleven months and fourteen months after injury showed a gradual transformation in the head proceeding largely from the fovea but to some extent from the distal fragment with irregular reduction in density, leaving a mottled spongy bone in more than four-fifths of the head but without any signs of collapse in the weight bearing portion of the cortex. The nonweight bearing portion laterally was replaced by bone casting a fainter and more even shadow than that in the weight bearing portion. The contour of the cortex of the head and the cartilage space of the joint are unaltered in outline.

The following case shows that when union occurs following intracapsular fracture with necrosis of the head, the ultimate result may be fairly satisfactory, although a clinical picture simulating chronic osteoarthritis of the hip joint may remain after several years have elapsed.

Fig. 35 (case 11 X).—Roentgenogram taken five years after fracture of neck showing union with reorganization and cavitation of the head with slight collapse in the weight bearing portion, which is evidence that the head was necrotic.

CASE 11 X (NECROTIC HEAD WITH UNION AND FAIR FUNCTIONAL RESULT)

A woman, aged 62, fell on the right hip, which produced pain and disability. A roentgenogram taken immediately was thought to show no fracture. She got up after four days and walked with a cane. The hip gradually became more painful, so that after four weeks she began to use crutches. As there was no improvement at the end of four months, another roentgenogram was taken which was reported to show a healed fracture of the neck of the femur. The hip continued to be painful and the patient used crutches for three years, then a cane for one year, but for one and a half years has walked unaided. She was examined five and a half years after the injury at which time she walked with a slight limp and complained of pain and weakness in the joint on walking long distances. Examination showed 1 inch of shortening of the right leg with moderate limitation of rotation and abduction and 50 per cent limitation

of flexion in the hip. A roentgenogram (fig. 35, case 11 X) showed a healed fracture with marked shortening of the neck of the femur and moderate coxa vara. The head shows evidences of marked reconstruction with the formation of large cavities and heavy irregular bony trabeculae in the weight bearing line. There is very slight collapse of the head along its weight bearing surface. The history and symptoms are consistent with an impacted fracture of the neck of the femur resulting in necrosis of the head and transformation and irregular replacement of the dead bone with little change in contour by ingrowing new bone under functional stimulation during the period when there was little or no weight bearing. The functional result was a fairly satisfactory one.

COMMENT ON CASES IN WHICH REUNION RESULTED DESPITE NECROTIC HEAD

It is therefore evident that necrosis of the head is not an absolute hindrance to bony union, as has been generally believed since the teachings of Köcher. Axhausen,[13] and later Bonn [14] thought that every complete intracapsular fracture of the neck of the femur results in necrosis of the head. The former stated that healing of the fracture in these cases is determined by the possibility of bridge formation between the fracture ends by the ingrowth of callus from the distal fragment, and revascularization and later organization of the head. It is beyond doubt that a bridge formation which at the start is made up of vascularized connective tissue and later callus may proceed exclusively from the distal fragment, as in Axhausen's case and cases 7, 9, 10, 11 and 11 X. In none of the cases here reported was there either histologic or roentgenologic evidence that callus forming in connection with blood vessels entering the necrotic head by way of the round ligament played a part in the healing of the fracture. Consequently, it must be concluded that when bony union occurs it is by way of new bone coming from the distal fragment. As Cornil and Coudray [21] have pointed out, there is necrosis of the cortex after fracture of any bone for a short distance back from the fracture line but that fact seems to play no more of a rôle in fractures here than elsewhere in the production of nonunion.

Organization of the necrotic head in case of union of the fracture proceeds from the tissues invading it from the distal fragment and in some cases from the round ligament. The rate of invasion of these tissues is variable, depending on the rapidity of union, the vascularity of the round ligament and the amount of functional stimulation from usage of the limb. As soon as union has occurred, usage hastens the rate of invasion of new tissue, of absorption of the necrotic tissue and of replacement by new-bone, bone-marrow and fibrous tissue. If there

21. Cornil, V., and Coudray, P.: Du cal au point de vue expérimentel et histologique, J. de l'anat. et de la physiol. **40**:113, 1904.

is too much weight bearing early as in case 10, there may be collapse of the weight bearing portion and marked deformity of the head before replacement of the dead bone and cartilage takes place with a poor functional result. If, however, the head does not bear too much weight but there is functional stimulation by movement without walking on the limb, transformation may occur with little or no collapse of the head, as in cases 11 and 11 X. The end-result is a head that shows much internal derangement but which functions fairly satisfactorily. In case 11, much of the transformation was brought about by invasion from the round ligament, as judged by repeated roentgenograms over a period of fourteen months. The "secondary arthritis deformans" in four out of thirteen cases reported by Portwich [22] was probably due largely to necrosis of the head with disintegrative changes. Johansson [23] reported collapse and absorption in the head beginning one to two years after healing of the fractures.

SURVIVAL OF HEAD

When, however, the femoral head remains alive after the fracture and the fragments are in good apposition, bony union of the fracture will occur in the great majority of cases. Being alive, the head will maintain its configuration and will not undergo secondary degenerative changes even long after the fracture has healed. This is illustrated by cases 12, 13 and 14.

CASE 12 (LIVE HEAD)

Case 12 is cited to indicate prompt healing of a fracture with no displacement or following early reposition of the fragments. Because the head was alive, as shown by its diffuse rarefaction in the roentgenogram taken three months after the injury, it did not undergo secondary degenerative changes during the period of four years following the healing of the fracture.

The patient was a woman who at the age of 71 slipped and fell on her left hip. This resulted in marked pain in the hip and disability. The roentgenogram taken at the time of the injury showed an impacted intracapsular fracture of the neck of the femur with slight displacement of the fragments. An ambulatory splint was worn for one month (fig. 36 *A*). The patient was then put in a cast for eight weeks; the cast was removed and another roentgen examination of the hip was made. This revealed bony union of the fracture with the neck in slight coxa vara (fig. 36 *B*). The head retained its normal contour and appeared to be alive, as was disclosed by its diffuse decrease in density. She was seen again almost a year and ten months after the bony healing of the fracture. She had good use of the limb and could go about her ordinary work without discomfort. A roentgenogram of the hip at this time disclosed a head that had maintained its configuration and was

22. Portwich, O.: Ergebnisse der unblutigen Behandlung medialer Schenkelhalsfrakturen, Deutsche Ztschr. f. Chir. **193**:145, 1925.

23. Johansson, S.: Ueber epiphysennekrose bei geheilten Collumfrakturen, Zentralbl. f. Chir. **54**:2214, 1927.

alive, as was manifest in the slight diffuse decrease in density. In spite of the coxa vara, the hip had three-fourths normal range of motion.

The patient was seen three years and ten months after the injury because of cancer of the cervix uteri. There was almost normal function and slight limitation of motion in the left hip.

A roentgenogram (fig. 36 *C*) showed the head still intact with bony trabeculae running into it from the distal fragment along the under surface of the neck. The

Fig. 36 (case 12).—*A*, roentgenogram taken two days after the injury and a day after application of ambulatory splints. *B*, roentgenographic appearance of the left hip three months after the injury, showing a healed intracapsular fracture of the neck. *C*, roentgenogram taken three years and eight months after the healing of the fracture. Note the diffuse decrease in density of the head, its normal shape and slight coxa vara. *D*, roentgenogram of a section of the femur showing bony repair of the fracture and newly formed weight bearing trabeculae in the head.

patient died of the carcinoma four and one-third years after the injury and the upper end of the left femur was obtained at autopsy. The neck was markedly shortened and the head was in the position of coxa vara. The stump of a small round ligament projected from the fovea. The articular cartilage was markedly thinned and yellow gray about the margins and fovea, but there was a band in between which was only moderately thinned and bluish. A coronal section showed a very short neck with union by dense bone along the fracture line. There had been absorption and replacement of the impacted neck fragments with laying down of new supporting trabeculae extending from trochanter minor along the bottom of the neck and upward to the top of the head, as shown in a roentgenogram of a slice of the specimen (36 *D*). Microscopic sections were made of the head, neck and trochanters. The head was alive but markedly atrophic. The articular cartilage was thin and at the margins and about the fovea it was overgrown and largely replaced by connective tissue. Blood vessels were present in the stump of the ligamentum teres. There was a dense bony intermediary callus. No dead bone was seen in the region of either neck or head.

CASE 13 (LIVE HEAD)

Case 13 indicates a head that apparently remained alive after the fracture. Prompt healing occurred following early reposition of the fragments. The head preserved its normal configuration three years after the fracture had healed.

The patient was a woman, 68 years old. Three years before examination, she fell on her right hip striking it against a stone pavement. She had to be carried to her home in a stretcher because of the acute disabling pain in her hip. Roentgen examination made on the day of the injury showed complete intracapsular fracture of the neck of the femur with slight separation of the fragments (fig. 37 *A*). With the patient under ether anesthesia, closed reduction was performed, and the leg was put in a double, long plaster of paris spica, in which it remained for eight weeks (fig. 37 *B*). The cast was then removed and another roentgen examination of the hip was made. This disclosed a good alinement of the fragments and bony union of the fracture. The head maintained its normal shape and appeared alive, as shown by the diffuse reduction of its density. The last time the patient was seen was three years after the injury; she was then free from discomfort in the hip. The result was excellent, as shown by the normal range of motion of the hip and by the roentgenogram taken at this time, which revealed healing of the fracture with slight coxa valga. Judging by the criteria herein established the head was alive and preserved its normal configuration (fig. 37 *C*).

CASE 14 (LIVE HEAD)

Case 14 indicates that when the head is alive and the fragments are in good apposition or impacted, a prompt healing of the fracture results in spite of failure to immobilize the hip. In such a case the head retains its normal configuration.

A woman, 54 years old, complained of slight soreness in the left hip which had been present for three months. Sixteen months before examination, she had fallen in the bathroom striking her hip against the edge of the bath tub. Every attempt to get up failed on account of the acute pain and disability of her hip. She was taken to her bed, where she remained for three days. The pain gradually

diminished in severity, and before the end of the week she was again able to be up and about. A roentgenogram taken two months after the injury showed a healed intracapsular fracture of the neck of the femur with impaction of the fragments (fig. 38). Manipulation followed by weekly vigorous massage was carried out for five weeks. After this time, the patient had increasing relief from discomfort until three months ago; then she again began to have slight soreness in the hip. Fearing that she might have a deforming arthritis in the hip,

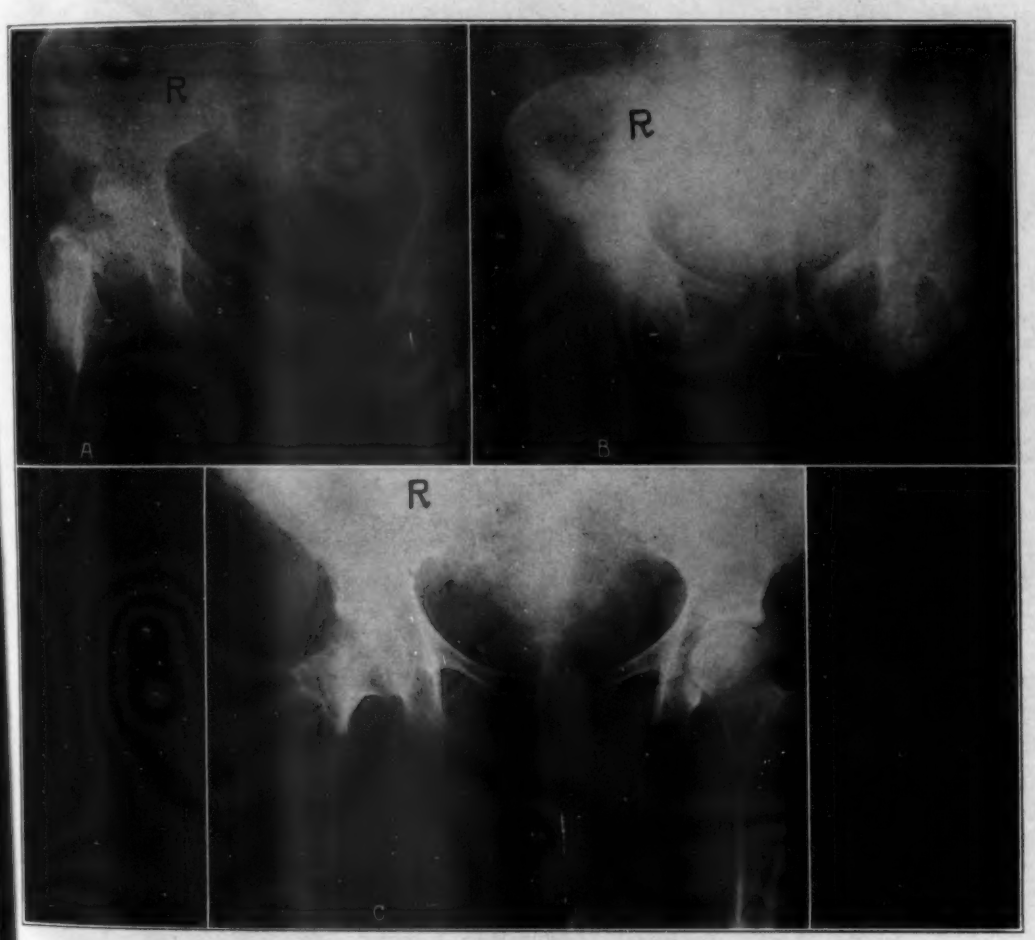


Fig. 37 (case 13).—*A*, roentgenographic appearance of the right hip on the day of injury. *B*, roentgenogram taken three days after closed reduction of the fragments. *C*, roentgenographic appearance of the right hip three years after the injury, showing a living femoral head which revealed slightly reduced density.

she came to the clinic for examination. The hip disclosed a full range of motion. No tenderness or disability could be elicited. Roentgen examination at the time, sixteen months after the injury, revealed a healed intracapsular fracture of the neck of the left femur (fig. 39). The femoral head showed normal shape and

Fig. 38 (case 14).—Roentgenogram taken two months after the injury, showing the healed intracapsular fracture of the neck of the left femur.

Fig. 39 (case 14).—Roentgenographic appearance of the left hip sixteen months after the injury. Note the healed fracture of the neck and the slight diffuse reduction in density of the head.

appeared alive but slightly atrophic, as shown by its slight diffuse decrease in density. Two years and four months after the injury the patient reported that the hip was free from pain and functioned normally except for slight limitation of motion.

When nonunion has existed for some time before open reduction and reposition of the fragments is performed, bony union of the fracture, if the head is alive, may still result in spite of marked atrophy of the fragments. This is well illustrated by the case reported by Henderson,[24] which indicates that a prompt anatomic healing of the fracture notwithstanding the existence of nonunion of more than three years' duration may occur with a good functional result (fig. 40). The marked diffuse

Fig. 40.—Successful bone graft for nonunion of more than three years' duration. Note partial restoration of the neck of the femur. The head is markedly atrophic with a small circumscribed area of reduced density about the fovea (after Henderson, Ann. Surg. **83**:696, 1926).

decrease in density of the head, as in cases 6 and 7, is evidence that the head was probably alive and as such did not undergo secondary degenerative changes but atrophied from disuse.

COMMENT ON CASES IN WHICH HEAD SURVIVED AND FRAGMENTS UNITED

In the three cases of intracapsular fracture of the neck of the femur in which the roentgenogram indicated that there was survival of the head and in which there was either impaction of the fragments or early reduction and fixation of fragments, bony union took place. The head

24. Henderson, M. S.: Ununited Fracture of the Hip, Ann. Surg. **83**:696, 1926.

retained its normal contour and its density varied with that of the surrounding bone showing reduced density from disuse at the end of the period of immobilization and a return to approximately a normal density after function was fully resumed. In case 12 coxa vara persisted, and new bony trabeculae were laid down across the head in the new lines of force. In cases 13 and 14 there was little change in the neck of the femur, and the head resumed almost normal appearance in roentgenograms.

The callus forms almost entirely in the intermediary zone, there being practically no new bone laid down on the surface of the neck. It appears to come from both fragments as is the case in the ordinary fracture. Bony union occurred in the one case of fracture with displacement of fragments following early reduction and fixation in abduction and internal rotation after the method of Whitman. However, there seems to be no good reason why nonunion should not occasionally result after good reduction and fixation of fracture of the neck with survival of the head as is the case with other fractures in various parts of the skeleton. In case of delayed or nonunion with survival and atrophy of the head of the femur it has been found that open operation with freshening of the fragments and fixation by a variety of procedures has been followed by bony union in a certain percentage of cases. This is exemplified in Henderson's case in which there was successful union after the use of a bone peg in a case of delayed union of three years' standing.

CAUSES OF NONUNION

There has been a great deal of controversy as to the causes of nonunion of fractures of the neck of the femur. They may be grouped broadly under four heads: (1) displacement of fragments, (2) excessive mobility of fragments, (3) necrosis of head of femur, (4) necrosis and erosion of neck fragments.

Exact reduction and fixation of fragments are undoubtedly the most important factors in obtaining bony union in case of intracapsular fractures of the neck of the femur as a group. This is shown by the variation in results that have been reported by different methods of treatment in which there have been variations in accuracy of reduction and degree and duration of fixation of fragments; also, by the great frequency with which bony union occurs in case of impacted fractures of the neck, when external fixation has been employed and sometimes when there has been no external fixation. It is generally conceded that the most efficient closed reduction and fixation of fragments is obtained by the Whitman abduction method of cast treatment. Portwich [22] reported thirty-one cases (67 per cent) of nonunion in fifty intracapsular fractures of the neck in which the Whitman abduction method was not used and only one case of nonunion among ten cases in which this method was used.

Campbell [25] treated twenty-nine fresh intracapsular fractures of the neck of the femur by the Whitman method, with bony union in twenty-four, nonunion in four, and in one the result was unknown. Of forty-four cases of ununited intracapsular fractures of the neck of the femur which came under his observation, Buck's extension was used in fourteen, plaster cast in nine, Hodgen's splint in four, sand bags in nine, osteopathy in two, ambulatory splint in one, and in five undiagnosed cases no treatment was given.

Necrosis of the head is undoubtedly an important cause of nonunion. When the circulation to the head is completely interrupted, the entire structure dies, and since the head and neck lie free in the joint there is no rapid attachment established with surrounding soft parts and consequently no survival of osteogenic elements along the fracture surface or periphery of the fragment-end such as occurs in a bone transplant located away from joints. Therefore, any callus that is formed for the repair of the fracture has to come from the distal fragment, and union between a completely necrotic and a living fragment is more difficult of accomplishment than between two living fragments. The slightest motion at the seat of fracture tends to break up the callus which has to bridge the defect and permeate, absorb and replace the dead bone. Of the fifteen cases here studied, there was complete necrosis of the head in nine and partial necrosis in one (case 7). Of these, there was nonunion in five cases, including the one case of partial necrosis, and bony union in the other five, including three cases in which nonoperative treatment was used, one case in which immediate beef bone pegging was performed, and one impacted case in which union was in the process of occurrence when death occurred on the twenty-fourth day. There was an impaction in two cases in which bony union was obtained, and in one case there was effective application of the Whitman abduction method of treatment. In one case of nonunion there was no treatment. In one case there was weight extension of the limb, and in two cases inefficient treatment was given with a plaster cast, as judged by the statement of the patient to the effect that the limb had not been fixed in marked abduction and internal rotation. The series is too small to judge of the exact frequency with which union takes place when the head is necrotic, but it would indicate that there is good opportunity for its occurrence in case there is impaction of fragments with external fixation or efficient reduction and fixation of fragments by the Whitman abduction method.

Erosion and absorption of the neck are factors that are secondary to the presence of nonunion and to movement of the fragments, whether the result of imperfect fixation or whether intentional after attempts at

25. Campbell, W. C.: Fractures of the Neck of the Femur, Ann. Surg. **70**: 600, 1919.

immobilization have been dispensed with. Lang [26] thought that absorption of the neck is the primary cause of nonunion and sought explanation for it in the poor blood supply in the middle portion of the neck. The bone which dies along the ends of the fragments, whether or not the head survives, is eventually absorbed and replaced by new bone as is the case with fractures in other locations. There is no particular reason to assume that it is absorbed more extensively without replacement by new bone in a fracture in this region than in other regions. In these cases there was about as frequent and as extensive erosion of the neck fragments in nonunion with survival of the head as in nonunion in the presence of necrosis of the head.

ROENTGEN RECOGNITION OF NECROTIC AND LIVING HEADS

Since the state of nutrition of the head of the femur has direct bearing on the occurrence of nonunion and of disintegrative changes in it and on the type of treatment that should be carried out, it is of great importance to try to estimate this as nearly as possible by means of roentgenograms. If the head remains alive, it will undergo the same degree of atrophy from loss of function produced by immobilization and of restitution produced by return of function as occurs in the neighboring bone of the ilium and distal fragment. Consequently, the head and the distal fragment show about the same degree of reduction in density at the end of the period of immobilization, and reduced density persists throughout the period of disability. In case of occurrence of bony union, there is a gradual return to original density with the full resumption of function. The arrangement of the newly deposited bone varies little from the normal except in case of union in coxa vara when shadows of heavy trabeculae will be seen along the new lines of force.

In case of nonunion and marked functional disability, as in case 6, there is persistence of uniform reduction in density of the head. When it becomes extreme as in cases of long standing, bony trabeculae may be entirely lost in relatively large areas of the head. Evidences of collapse and disintegration of the weight bearing portion of the femur are not seen regardless of the degree of atrophy that may develop. The shadows cast by the fragment of the neck in case of nonunion are gradually lost as erosion progresses.

In case of necrosis of the proximal fragment there is a distinct difference in density between the shadow cast by the head and the neighboring living bone at the end of the period of immobilization treatment. This difference is visible at the end of six weeks and is usually marked at the end of two and one-half or three months. The head, having lost its blood supply, has been unable to atrophy and casts a shadow of nor-

26. Lang, A.: Beiträge zur Lehre von den Schenkelhalsbrüchen auf Grund anatomischer und klinischer Studien, Deutsche Ztschr. f. Chir. **135**:101, 1916.

mal density while the neighboring living bone casts a shadow of reduced density as a result of atrophy of disuse. Subsequent changes in density in both head and neighboring bone vary according to whether or not bony union occurs and according to the use that is made of the limb. If there is nonunion, the neighboring living bone continues to cast a shadow of reduced density due to the protracted disuse. The necrotic head is more or less gradually invaded by blood vessels and connective tissue, but in the absence of functional stimulation there is very slow absorption of the dead bone with partial replacement by living bone. Consequently, it continues to cast a heavier shadow than the neighboring atrophic living bone for a prolonged period. In cases 2 and 3, the heads still cast uniformly dense shadows at the end of sixteen and thirteen months, respectively. The histologic evidences of absorption and beginning replacement by spongy bone and the roentgenologic evidence in cases 2 and 7 would indicate that a gradual irregular reduction in density in the ununited necrotic head is brought about in the course of years. Consequently, in cases of nonunion of long standing it should be difficult to distinguish between the cases in which the head remained alive and became atrophic, and those in which the head underwent necrosis with slowly progressive absorption and partial replacement by living bone. In general, the transformed necrotic head would be expected to cast a more blotchy and uneven shadow than the atrophied living head.

When there is necrosis of the head and bony union of the fracture occurs, the necrotic head casts a heavier shadow than the distal fragment at the end of the period of immobilization. With the resumption of function, the tissues of the distal fragment and in some instances of the round ligament are stimulated to invade the necrotic head with resultant absorption and replacement by new bone at a much more rapid pace than occurs when there is no functional stimulation as in the case of nonunion. This transformation is evidenced by an irregular reduction in density proceeding from the fracture line where the invasion is from the distal fragment and from the fovea where the invasion is from the round ligament. If the head is protected from too extensive weight bearing, its normal uniform density is gradually replaced by a more or less unevenly reduced density with little or no change in its contour. This is illustrated in cases 11 and 11 X. With the resumption of extensive weight bearing following this extensive replacement of necrotic bone by living bone, the head greatly increases in density but the outline of the new bone is irregular and blotchy, as shown in figure 35, case 11 X.

In case of necrosis of the head in which bony union occurs and there is too much weight bearing before invasion, and transformation of the necrotic bone has been brought about, the weight bearing portion of the head will show evidence of collapse in the roentgenogram with a depression of its articular surface and irregular dense shadows in the underlying bone due to compression of the broken-down necrotic trabeculae.

Invasion of the neck from the distal fragment results in irregular reduction in its density with abnormally arranged shadows of newly formed bone. In case 10, the greater part of the head had its density reduced as a result of rapid transformation during the eight and one-half months following the injury, and the nonweight bearing portion continued to cast a faint shadow during the subsequent three years due to the fact that motion in the hip was markedly limited and weight was not borne on it. Collapse and extensive irregular transformation in the weight bearing portion of the head of the femur after healing of the fracture of the neck is always indicative of necrosis of the proximal fragment. The condition is not one, as Axhausen thought, of arthritis deformans in the true meaning of the term.

BEARING OF OBSERVATIONS ON TREATMENT

The objective in the treatment of all fresh fractures of the neck of the femur, whether the head survives or becomes necrotic, should be to secure bony union with as nearly complete reduction of fragments as it is possible to obtain. This is best accomplished by means of the Whitman abduction and internal rotation method of cast treatment. The cast should be removed in from ten to twelve weeks, as this is usually adequate time, whether the head is dead or alive, for the occurrence of bony union although from four to six months may be necessary for it to become solid. From roentgenograms taken at the end of this time it should usually be possible to say whether the head survived or became necrotic; also, whether or not the fracture is united. When there is doubt about these points, a second or third roentgen examination after a few days or weeks will usually clear them up. When it is determined that the fracture is united and that the head remained alive, the patient should be allowed to go about on crutches, and in from one to two months begin weight bearing. Collapse of a surviving head from subsequent weight bearing has not been reported.

On the other hand, if it is found that the fracture is united and that the head became necrotic, the resumption of function should be very much more gradual than when the head survives. The patient should walk with crutches, and weight bearing should be delayed for several months, from six to twelve, in order to allow time for the invasion and replacement of the necrotic bone by living bone and to avoid possible collapse of the weight bearing portion and deformity of the head with a bad functional result. A necrotic head with bony union usually produces a more painful hip than a living head, and weight bearing cannot be tolerated for some time. Hence, collapse does not usually occur although the patient is privileged to walk on the limb. The progress of transformation in the head may be followed in the roentgenogram as

in case 10 and the appropriate time for discarding crutches judged accordingly. Movement of the limb without weight bearing should be encouraged, as functional stimulation hastens the rate of transformation of the head. If a patient is seen in whom slight or moderate collapse has occurred, weight bearing should be discontinued and an opportunity given for organization of the head. If the collapse and deformity are marked, there may be extensive disability resembling arthritis deformans, and a Whitman reconstruction operation with excision of the deformed head may be indicated.

If there is nonunion with survival of the head and the patient is a good operative risk, there is some question as to the best plan of treatment. In case the injury is not too old, the fragments of the neck not extensively eroded and good approximation of freshened fragments can be obtained, the bone pegging operation of Albee may be indicated. If the case is of several years standing or if the neck has been eroded, either the Whitman or the Brackett reconstruction operations should be performed. If the fracture is ununited and the head has undergone necrosis the best procedure, when the patient's symptoms and general condition warrant operation, would appear to be the Whitman reconstruction operation of excision of the head, insertion of the upper end of the shaft in the acetabulum with displacement of the trochanter downward and attachment to the side of the shaft. Either the bone pegging or the Brackett operation would be expected to result in a high percentage of nonunion, and even if union occurred, stiffness and a deformed head would be likely to give a poorer functional result than the Whitman operation. In the case of necrosis of the head of long standing with revascularization and partial or complete replacement by new bone, a Brackett or bone pegging operation would probably give a poor result here either from adhesions or from nonunion.

SUMMARY

The only source of blood supply to the head in case of complete intracapsular fracture of the neck of the femur is the ligamentum teres, and the extent of the vessels contained in it at the time of occurrence of the fracture determines its subsequent vitality. If the vessels are adequate, the head remains alive, but if inadequate it undergoes necrosis. While the blood vessels are more abundant in younger persons, they may be adequate to keep the head alive after fracture in the aged. The necrosis involved the entire head in all of the cases in which it occurred except one. The relative frequency of living and necrotic heads after fracture of the neck cannot be judged from the fifteen cases here reported (six living and nine necrotic) since most of them were selected because of the fact that they afforded material for pathologic study or because of

the presence of special features, as nonunion, necrosis of the head with bony union, or survival of the head with bony union in the aged. However, it is evident that necrosis of the head is a not uncommon occurrence.

When the head remains alive, there may be either bony union or nonunion of the fracture. Bony union occurs in a large percentage of cases if the fracture is well reduced and immobilized by the Whitman abduction method or if it is put at rest in case of impaction. Nonunion is the usual result of faulty reduction and fixation although it may follow efficient reduction and fixation as is sometimes the case in fractures in other locations. When the head survives and union occurs, it undergoes atrophy of disuse during the period of immobilization and subsequent disability and regains its normal bony density with the restoration of function. It never collapses subsequently from weight bearing, but when there is nonunion the head usually remains permanently atrophic. The articular cartilage is thinned by absorption along its attachment to bone and may be partly replaced by bon-marrow and new bone.

In case of inadequate nutrition of the proximal fragment through the round ligament, the bone, bone-marrow and cartilage become necrotic. Bony union may follow in case of efficient reduction and immobilization or in case of impaction. In this event, the head is gradually invaded by tissue growing across the healing fracture from the distal fragment, and in some cases from the hypertrophied round ligament, the dead bone, bone-marrow and cartilage are absorbed and more or less completely replaced by irregularly distributed new bone, bone-marrow and fibrous tissue. The weight bearing portion of the head may collapse before the result, but the prolonged avoidance of weight bearing may prevent this occurrence and a good functional result may be obtained.

Necrosis of the head predisposes to nonunion. When the fracture, after a period of treatment, remains ununited, the head is denser and casts a heavier shadow in roentgenograms than the surrounding living bone which has undergone atrophy. The necrotic head may be gradually invaded by newly formed tissue from the round ligament and from adhesions which form between the capsule and the eroded fracture surface. This tissue gradually replaces the necrotic marrow and absorbs the dead articular cartilage. Replacement of the dead bone by living bone takes place at a very slow rate. Consequently, the head may remain denser than the neighboring atrophied bone for at least from one to two years as seen in cases 2 and 3. The absence of active functional stimulation explains the slow rate of transformation in the head as compared with that which is seen in case of necrosis of the head followed by bony union. In the absence of weight bearing there is no collapse of the head as shown by a roentgenogram, but compression of it between trochanter and

acetabulum may lead to some erosion of necrotic articular cartilage and breaking down of subcortical trabeculae as seen in case 3.

It should usually be possible by means of roentgenograms to tell after from six to ten weeks have elapsed whether the head is dead or alive in the event of either union or nonunion. The living head undergoes more or less uniform atrophy of disuse and in case of return of function it maintains the original density for a long period of time. Its density dead tissue has been absorbed and replaced, giving a poor functional may eventually become uneven and blotchy as a result of invasion, absorption and replacement by new bone. Collapse and deformity developing after union has occurred is always indicative of necrosis of the head.

It would appear from these observations and from other published reports that all fresh fractures of the neck of the femur are best treated by Whitman's reduction and abduction cast fixation. If bony union follows with survival of the head, there is usually restoration of satisfactory function within a period of a few months. If bony union follows with necrosis of the head a painful hip may persist or may return after usage. Weight should not be borne on the head for many months in order to allow sufficient time for creeping substitution of the necrotic head by new bone and thereby prevent possible collapse and deformity of the head. If nonunion occurs and the head remains alive the choice of treatment in a patient who is a good operative risk lies between an autogenous bone peg and a Whitman or a Brackett reconstruction operation depending on the changes in each case. If the head is necrotic and nonunion results, a Whitman reconstruction operation should be performed.

CONCLUSIONS

1. After complete intracapsular fracture of the neck of the femur, the proximal fragment may either remain alive as a result of nourishment received through the vessels of the ligamentum teres or become necrotic.

2. If efficient reduction and fixation are carried out early and sufficiently long maintained, bony union follows in a high percentage of the cases in which the head remains alive and in a smaller but no inconsiderable percentage of cases in which the head becomes necrotic.

3. If bony union occurs in the presence of necrosis of the proximal fragment, the limb should be protected from weight bearing for many months while creeping substitution of dead head by new bone is taking place. If marked collapse and deformity of the necrotic head should develop, a Whitman reconstruction operation with excision of the head may sometimes be indicated.

4. If nonunion results and the head remains alive, a patient who is a good risk may be operated on by use of an autogenous bone peg or by the Whitman or the Brackett reconstruction method according to the case.

5. In case of nonunion with necrosis of the head, there may be slow invasion of tissue from the round ligament or from adhesions with very gradual absorption and partial replacement of the necrotic tissue by living bony elements. However, the proper operative treatment in case of nonunion with necrosis of the proximal fragment appears to be excision of the head and the performance of a Whitman reconstruction operation.

6. By roentgenographic studies, it is usually possible to differentiate between a head that remains alive and one that becomes necrotic because of their difference in density which develops during the period of disuse and because of their difference in internal structure and occasionally in contour which develops during the period of reconstruction.

A COMPARISON BETWEEN SIMULTANEOUS EQUAL-SIZED CLOSED OBSTRUCTIONS OF THE DUODENUM AND THE ILEUM*

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In a previous study,[1] it was indicated that there were marked anatomic and physiologic differences between obstructed loops of the duodenum and of the ileum in the dog. The anatomic observations have been in a large measure corroborated by Dragstedt, Lang and Millet.[2] These investigators showed that distention of the intestine caused the greatest interference in the duodenum because of the anatomic distribution of the blood vessels in the duodenal wall.

We have nothing new to add to our anatomic studies already reported, but wish to record some additional data on the secretion rates, intraintestinal pressures, distensibilities, and bursting pressures of equal-sized loops of the duodenum and ileum.

EXPERIMENTAL WORK

Dogs were anesthetized with ether, and simultaneous closed loops of equal size were made in the terminal duodenum and in the terminal ileum. This procedure was carried out by finding the duodenojejunal ligament and tying a flat tape tightly across the lumen of the duodenum without damaging the blood supply in the mesentery. Ten centimeters were then measured up the duodenum, and a second tape was passed around the bowel and tied tightly. This made a closed loop of terminal duodenum from which gastric, pancreatic and biliary secretions were excluded. In the same way the 10 cm. segment of terminal ileum was

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* From the Department of Surgery, the University of Rochester School of Medicine and Dentistry.

* Aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Morton, J. J.: The Differences Between High and Low Intestinal Obstruction in the Dog: An Anatomic and Physiologic Explanation, Arch. Surg. **18**:1119 (April) 1929.

2. Dragstedt, C. A.; Lang, V. F., and Millet, R. F.: The Relative Effects of Distention on Different Portions of the Intestine, Arch. Surg. **18**:2257 (June) 1929.

measured off from the ileocecal junction and occluded (fig. 1). The animals were anesthetized every twenty-four hours, and the contents of the closed loops were aspirated with a needle and syringe. After the contents were measured carefully, they were returned to the loop from which they had been withdrawn. In this way it was hoped to get an accurate measure of the secretion rate without disturbing the abnormal intra-intestinal pressure relations which had occurred. Eight animals were

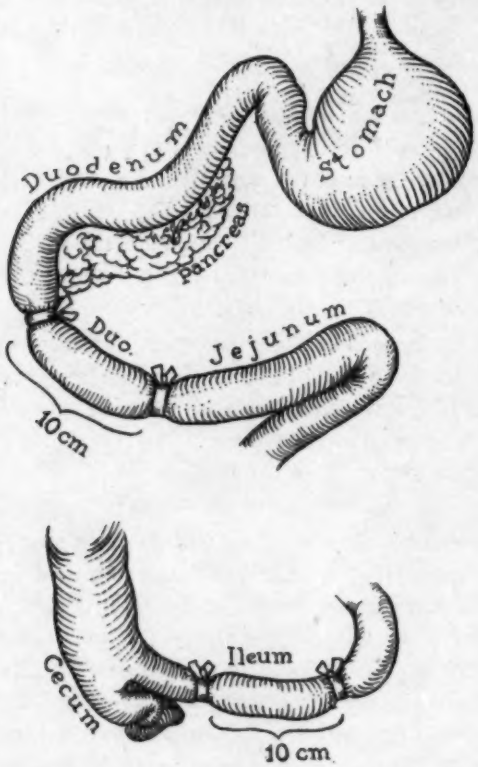

Fig. 1.—Diagram showing closed loops of equal size which were made in the terminal duodenum and terminal ileum.

used for this part of the experiment, and the results are recorded in in table 1.

There is a striking difference in the amount of secretion which accumulates in the closed duodenal and in the ileal loops. The secretory rate for the ileum is practically negligible, the amount even after seventy-two hours being only approximately 1 cc. In the duodenum, on the contrary, there is a rapid production of fluid so that the average reading for the eight animals at twenty-four hours was 11.3 cc. The secretion mounts sharply in the second twenty-four hours, averaging

35.7 cc. for seven animals at the end of forty-eight hours. During the third day following, the pressure becomes so great as to rupture the duodenal loop at the occluding tape or through the puncture holes. We do not believe that the measured quantities obtained at seventy-two hours represent the actual amount secreted in spite of the fairly high figures, because a majority of the animals already show leakage at this

TABLE 1.—*Amount of Secretion in Closed High and Low Loops in Cubic Centimeters Compared with Toxicity as Measured by Blood Chemistry in Milligrams per Hundred Cubic Centimeters*

Dog Number		Time of Operation	24 Hours	48 Hours	72 Hours	Observations at Autopsy
27-288	Duodenum	0	5	20	...	Died 60 hours after operation; small leak in duodenum; ileum intact, 2.5 cc. found.
	Ileum	0	0.5	2.5	...	
	Nonprotein nitrogen	26	...	97	...	
	Chloride	490	...	320	...	
28-110	Duodenum	0	10	40	60	Died 72 hours after operation; rupture duodenum; general peritonitis; ileum intact
	Ileum	0	1	1	1	
	Nonprotein nitrogen	27.5	35.3	80	158	
	Chloride	515	465	418	380	
28-131	Duodenum	0	2.5	35	...	Died 60 hours after operation; leak in duodenum; ileum intact; general peritonitis
	Ileum	0	0.2	0.5	...	
	Nonprotein nitrogen	28	30.8	38.7	...	
	Chloride	490	430	369	...	
28-92	Duodenum	0	3	20	...	Died 50 hours after operation; leak in duodenum; general peritonitis
	Ileum	0	0	2	...	
	Nonprotein nitrogen	25	31	72	...	
	Chloride	490	450	279	...	
28-148	Duodenum	0	5	...	30	Died 90 hours after operation; leak in duodenum; ileum intact; general peritonitis
	Ileum	0	0.5	...	2	
	Nonprotein nitrogen	...	...	...	...	
	Chloride	...	...	...	...	
28-161	Duodenum	0	42	70	75	Leaked at puncture hole; free fluid; fresh peritonitis; died 72 hours after operation; very large dog
	Ileum	0	0	0.5	0.5	
	Nonprotein nitrogen	31	40	66	133	
	Chloride	480	465	390	330	
28-210	Duodenum	0	15	50	60	Localized peritonitis; free fluid; fresh general peritonitis; died 72 hours after operation; large dog
	Ileum	0	0.5	0.5	0.5	
	Nonprotein nitrogen	33	30	80	120	
	Chloride	440	390	445	350	
29-220	Duodenum	0	8	15	20	Localized peritonitis; leak around puncture hole; fresh general peritonitis; died 80 hours after operation
	Ileum	0	0	0.5	0.5	
	Nonprotein nitrogen	36	37	48	90	
	Chloride	490	465	355	320	
Average figures for the series	Duodenum	0	11.3	35.7	49	
	Ileum	0	0.33	1.07	0.9	

time. A comparison of the secretion rates in the duodenum and ileum can be easier appreciated by observing figure 2, which is a graph of the average figures for the series. This study also brings out the essential differences in function between the duodenum and the ileum. Physiologists have long taught that absorption occurs in the ileum and that the most active secretion takes place high in the small intestine. It would appear from these experiments that this is true, and that the current is toward the lumen of the bowel in the duodenum and away from it in the ileum.

The average length of life for twelve animals with this type of double closed loop obstruction was approximately seventy-one hours.

It is interesting to note that the animal which lived the longest of the group—ninety hours—had a low secretion in the duodenal loop, only 30 cc. being present at seventy-two hours. Another animal, which died eighty hours after operation, had only 20 cc. of fluid in the duodenum at seventy-two hours. These figures are well below the average for forty-eight hours. Without exception death was due to peritonitis and the leak occurred in the duodenal segment. It is probable that the high obstruction is alone responsible for the outcome in these animals. If it were not for the rupture and peritonitis, the animals might survive for a much longer period. This observation lends support to the contention of Chenut,[3] who claimed that the toxic products are absorbed

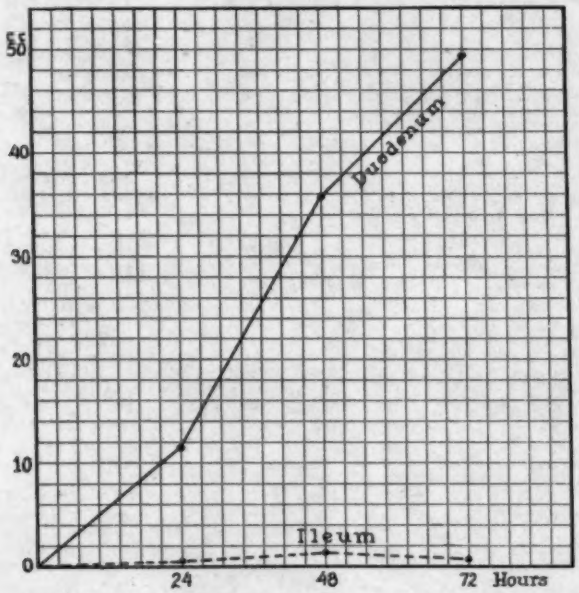

Fig. 2.—A comparison of the secretion rates of equal-sized closed segments of duodenum and ileum.

through the peritoneum, and that absorption is practically nil when the obstructed loops are put in an extraperitoneal position. It also raises the question whether any toxin is ever absorbed through the intact wall of the bowel.

Six animals were used for a study of the intra-enteric pressures developed in these closed segments. A water manometer, as originally described by Owings, McIntosh, Stone and Weinberg [4] was used. The

3. Chenut, A.: L'expérimentation dans l'occlusion méchanique de jejuno-ileon, Rev. de chir. **64**:474, 1926.

4. Owings, J. C.; McIntosh, C. A.; Stone, H. B., and Weinberg, J. A.: Intra-Intestinal Pressure in Obstruction, Arch. Surg. **17**:507 (Aug.) 1928.

measurements show a great variation, depending on the state of the intestine at the time. The peristaltic waves cause decided increases in pressure, and it is difficult to judge the exact end point for any reading. In general, the sustained pressures in the duodenum were slightly higher than in the ileum just after operation. Within the first twenty-four hours the pressure, sustained and peristaltic, mounted steadily in the duodenal segment until it was from four to seven times as great as in the ileum. There was a slow rise also in the pressure within the ileum. In the second twenty-four hours the pressures in the duodenum were not so striking. We feel that technical difficulties with the apparatus failed to bring out the differences that must have been present. We consider that the readings for the first twenty-four hours were an index

TABLE 2.—*Difference in Intra-Intestinal Pressure Measured in Millimeters of Water in Obstructed Closed High and Low Loops*

Dog Number		Operation	4 Hrs.	8 Hrs.	12 Hrs.	16 Hrs.	20 Hrs.	24 Hrs.	48 Hrs.	72 Hrs.	Cause of Death
27-217	Duodenum	100-120	110-140	240-310	..	...	...	210-520	...	...	Died suddenly; 24
	Ileum	5	5	20	..	...	...	80	...	...	hours; peritonitis
28-130	Duodenum	55	..	..	..	...	...	280-350	120-170	...	Dog chloroformed;
	Ileum	50	..	..	..	...	...	50	60	...	localized peritonitis
28-207	Duodenum	30	..	30	70	100	130-160	250-370	200-300	180-250	Localized peritoni-
	Ileum	20	..	20	20	20	20	40	170	270	tis and early diffuse peritonitis
28-219	Duodenum	40	50	..	90	...	...	150-400	160-230	...	Diffuse peritonitis;
	Ileum	20	20	..	20	...	...	50	70	...	died 52 hours
28-284	Duodenum	20	20	20-30	..	80	100	100	150	70-80	Died 80 hours;
	Ileum	20	20	20	..	30	30	40	100	140	localized and diffuse peritonitis
28-148	Duodenum	20-30	..	..	..	...	...	40-100	...	160-200	Died 80 hours; gen-
	Ileum	10	..	..	..	..	...	10	...	50	eral peritonitis

of the real differential pressures in the two loops; but our later readings do not indicate the true state of affairs. In several of our animals there was an early leakage of material around the stem of the duodenal cannula, and perhaps this accounts for the poor results. Possibly the caliber of the manometer was too gross to register the values accurately. The results of these pressure measurements are given in table 2. Photographs of manometer pressure records are also shown (fig. 3).

A great many measurements were made to test the amount of distensibility in length and circumference of segments of the duodenum and the ileum. These observations were taken while finding the amount of air pressure necessary to determine the bursting pressures of the segments. Table 3 shows the observations on the segments tested immediately and one, two, four and twenty-four hours after death.

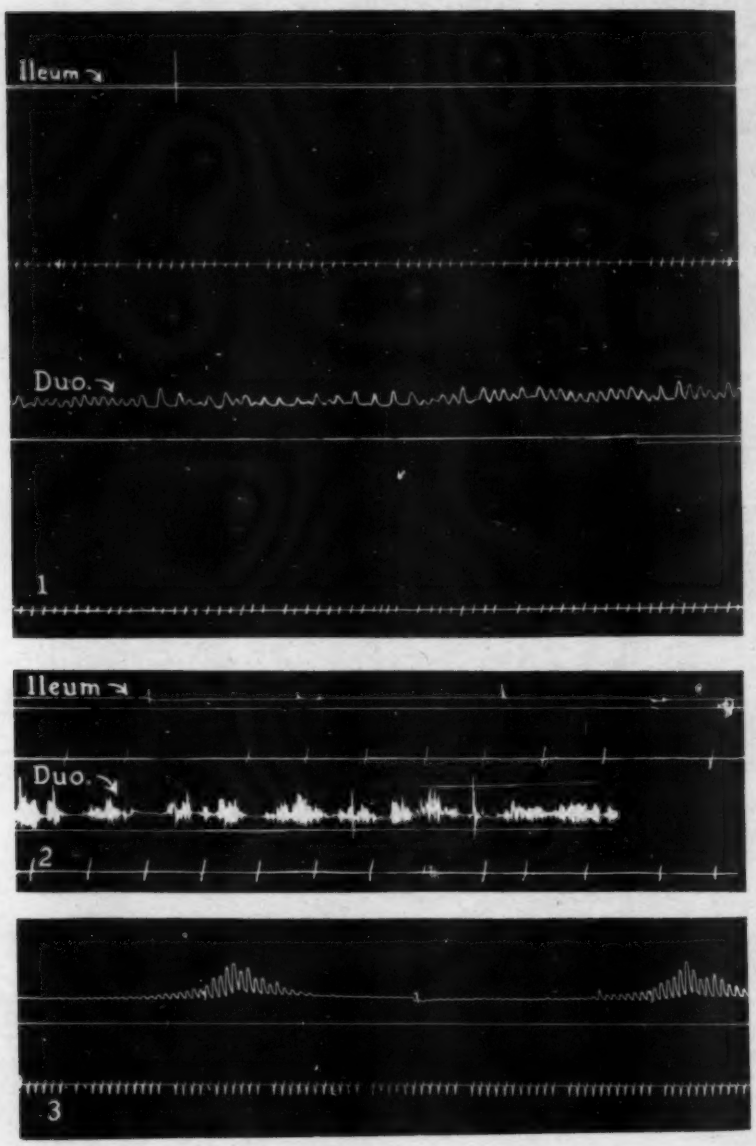

Fig. 3.—Illustrations showing (1) obstructed loops of duodenum and ileum at twenty-eight hours; time interval, five seconds. The ileum is inert, but the duodenum has continuous peristalsis at a fairly high pressure; (2) obstructed loops of duodenum and ileum at forty-eight hours; time interval, one minute; (3) obstructed duodenum at twenty-four hours; time interval, five seconds. The peristaltic waves are well shown in addition to the substained pressure above the base line.

Practically all the tests made were similar to these readings. The immediate samples indicate the wide range of variation in distensibility in length and width, and the great amount of elasticity of the segments. A pressure over 1,000 mm. of mercury was necessary before rupture occurred. The ileum seemed to possess a greater lengthening power than the duodenum, but the distention in circumference was about equal. The powerful duodenal musculature made the duodenal segments able to withstand a somewhat greater pressure. In even as short a period as one hour after death the elasticity of the segments seemed to be altered. The stiffening due to rigor was best demonstrated by the burst-

TABLE 3.—*Segments Immediately, One, Two, Four and Twenty-Four Hours After Death*

Dog Number		Segment	Length in Cm. Normal	Length in Cm. Complete Distention	Circumference in Cm. Normal	Circumference in Cm. Complete Distention	Pressure Mm. Mercury	Point Rupture
28-98		Duodenum	6.5	12.0	5.0	7.5	1500	Antimesenteric small hole
	Immediately	Ileum	9.0	23.0	4.0	7.0	1200	Blew end off
	after death		9.0	21.0	4.0	5.5	1050	Blew end off
6		Duodenum	7.0	9.5	4.0	7.5	1400	Antimesenteric wide hole
	Immediately	Ileum	10.0	12.0	3.0	6.5	1080	Antimesenteric small hole
	after death		9.0	11.5	3.0	5.0	1175	Antimesenteric small hole
7		Duodenum	10.0	14.0	5.0	8.0	725	Antimesenteric
		Ileum	10.0	17.5	3.5	7.0	800	Antimesenteric
	Dead 1 hour		10.0	17.75	3.5	7.5	790	Antimesenteric
4		Duodenum	10.5	13.0	4.3	9.5	800	Antimesenteric end blew off
		Ileum	11.0	13.0	2.2	7.5	500	Wide hole mesentery
	Dead 2 hours		10.0	13.0	2.3	6.0	680	Wide hole mesentery
3		Duodenum	10.0	13.0	5.0	9.0	900	Antimesenteric
		Ileum	10.0	16.0	4.0	8.5	770	Wide hole antimesenteric
	Dead 4 hours		10.0	16.0	4.0	9.5	760	Wide hole antimesenteric
5		Duodenum	10.0	11.0	3.5	7.5	830	Blew end off antimesenteric
		Ileum	10.0	10.5	3.0	5.75	700	Blew end off
	Dead 24 hours		11.0	12.0	3.0	5.0	690	Blew end off

ing pressures, the average of the readings being only about 750 mm. of mercury, as against nearly double the figure for the specimens tested immediately.

The results of this study confirm our previous observations on the physiologic differences between the high and the low obstructions in the dog. The most striking phenomenon is the rapidly increasing secretion in the duodenal segment, in contrast to the comparatively inert secretion in the segment of the ileum. The increase in fluid content is naturally accompanied by a raised intra-enteric pressure which is well demonstrated at the end of the first day after operation. This

increase in pressure within the upper segments is apparent in the following days as well, but in these experiments technical difficulties, leakage, etc., masked the undoubtedly much greater hydrostatic pressures in the duodenum. Rupture always occurred in the duodenal segment, and death was invariably due to peritonitis. Studies are at present in progress to test further the physiologic differences in high and low intestinal obstructions.

FORTY-SECOND REPORT OF PROGRESS IN ORTHOPEDIC SURGERY *

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CONGENITAL DEFORMITIES

Torticollis.—Howell [1] operated on twenty patients by means of a subcutaneous tenotomy of the sternal head of the sternomastoid muscle, with nineteen complete cures. He used a plaster of paris cast for four weeks; this was then bivalved and retained for another four weeks. Treatment by a masseuse completed the cure in from three to six months.

[ED. NOTE.—The tenotomy of the sternal portion alone seems to us inadequate in many cases. The simplicity of the open operation hardly warrants the risk entailed in a subcutaneous operation.]

Congenital Dislocation of the Hip.—Fairbank [2] chose congenital dislocation of the hip as the subject for the Lady Jones lecture at Liverpool in 1929. The first half of the lecture he devoted to pathologic anatomy,

* This Report of Progress is based on a review of 226 articles selected from 638 titles dealing with orthopedic surgery appearing in the medical literature between Nov. 30, 1929, and May 1, 1930. Only those papers which seem to represent progress have been selected for note and comment.

1. Howell, B. W.: Brit. M. J. **2**:714 (Oct. 19) 1929.

2. Fairbank, H. A. T.: Brit. J. Surg. **17**:380, 1930.

basing his remarks on experience in fifty open operations on the hip joint and on a study of thirty-six specimens, many of which repose in Dupuytren's Museum in Paris and are beautifully reproduced in the paper.

The anatomic changes in the pelvis, bones, ligaments and muscles were reviewed in detail. Fairbank left his readers to draw their own inferences from this mass of pathologic anatomy. It would seem that the prime cause of the dislocation was the poor development of the upper rim of the acetabulum, and that this factor was further responsible for the prolonged immobilization required after reduction. The difficulties of reduction were due (1) to diminution in the size of the acetabulum, which after a few years became triangular because of the unresisted overgrowth of the anterosuperior and posterior margins, and (2) to a narrowing of the capsule between the true and false acetabulum socket. This isthmus owed its origin to factors both outside and inside the capsule. The narrowing within the capsule was caused by a horizontal fold of a synovial membrane situated at the level of the true acetabulum. This fold was flattened out when the head of the femur rode up on the ilium and folded up into a band when the head was pulled down toward the true acetabulum, thus impeding its progress. The narrowing without the capsule was caused by the constriction of the iliopsoas tendon, which became more taut when the head of the femur was pulled down and so offered an obstruction to reduction. These facts pointed to the choice of the Denucé method of reduction in preference to the Lorenz method. In addition to the diminution in the size of the acetabulum and to the presence of the isthmus, a third difficulty of reduction existed, namely, the shortening of the adductor muscles, which it was necessary to stretch or rupture prior to reduction.

In the second half of the lecture Fairbank discussed the causation of the limp, the reason for pain in unreduced dislocations, and treatment. He considered that the limp, though made worse by the shortening of the limb, was due (1) to diminution in the power of abductors because of the restriction of the area of the ileum from which the muscles could arise, (2) to diminution in the leverage of the abductor muscles owing to the position of the head of the femur, (3) to the relative weakness of the abductors because of the simultaneous powerful contraction of the adductors in their endeavor to transmit the weight of the body from the pelvis to the leg and (4) to the instability of the fulcrum which allowed the head of the femur to ride up and down and backward and forward on the ilium.

The aim of treatment, according to Fairbank, was twofold: to provide a stable joint and to prevent subsequent arthritis. Reduction at an early age alone would ensure this double success. In the older patient

stability might be achieved by reduction, but it was unlikely that arthritis would be avoided; for this reason Fairbank did not attempt to reduce a bilateral dislocation in patients more than 6 years of age, or a unilateral dislocation in patients over 9.

Fairbank resorted to open reduction only after closed reduction had failed; if he had to operate, whether reduction was successful or not, he always made a new roof by turning down a bone shelf. In his belief, antetorsion sufficient to demand osteotomy or to cause a redislocation was rare. He considered failure of the upper lip of the acetabulum to grow out a more potent factor leading to redislocation, and when the hip redislocated in spite of efficient after-fixation, he advocated making a new shelf. He did not approve of transposition in irreducible cases, a procedure that he found difficult to use and one that was frequently followed by relapse. For the irreducible case in which increasing disability and pain developed in adolescent or adult life, he advocated arthrodesis of the hip on the affected side in unilateral cases and on the worse side in bilateral cases; but he warned against fusing the joint in too much abduction. Osteotomy might be of value in a few selected cases in which the pain was due, not to arthritis of the joint, but to strain on ligaments and muscle weakness. He had no experience with the shelf operation advocated by Dickson and Allison, nor did he like excision of the head for old unreduced dislocations.

[ED. NOTE.—The editors regard this general discussion as excellent in its general exposition of the question. They would be more inclined to favor the shelf operation in the irreducible cases in preference to arthrodesis.]

Mandruzzatto,[3] reporting the statistics on treatment for congenital dislocation of the hip at the Instituto Orthopedico Rizzoli from 1899 to 1927, stated that he found 3,685 dislocations in 2,578 patients. Of these patients, 85.02 per cent were females and 14.58 per cent, males. There were 42.94 per cent bilateral and 57.06 per cent unilateral dislocations. Of the latter group, 39.02 per cent were on the right side and 21.83 per cent on the left. In females, bilateral dislocation was found in 36.96 per cent: on the right side in 29.82 per cent and on the left in 17.72 per cent. In males, bilateral dislocation was found in 5.97 per cent: on the right side in 5.39 per cent and on the left in 4.11 per cent.

[ED. NOTE.—The percentages are of total cases in males and females.]

Information in regard to heredity and familial tendency was obtained in 2,276 of the 2,578 cases. Direct heredity was found in 6.54 per cent and was slightly greater on the male side. A familial tendency was found in 16.69 per cent of the cases and was definitely more marked on

3. Mandruzzato, F.: Chir. d. org. di movimento **14**:200, 1929.

the male side. There was nothing to indicate that delivery had any definite rôle in the etiology. Concomitant deformities occurred in 3.04 per cent of the cases.

In the 2,578 cases diagnosis was made during the following age periods: before 1 year in 2.32 per cent; from 1 to 3 years in 47.36 per cent; from 3 to 6, in 29.36 per cent; from 6 to 10, in 9.65 per cent; from 10 to 15, in 5.77 per cent, and after 15 years in 5.54 per cent. The statistics showed that diagnosis is constantly being made at an earlier age.

The treatment was bloodless reduction by the Paci-Lorenz method in 88.48 per cent of the cases. Open reduction was performed in 3.16 per cent and some form of reconstruction in 3.08 per cent. The statistics further showed that there was a regional distribution of the cases.

[ED. NOTE.—These statistics from such an important clinic in the treatment for this particular condition are significant. We regret that they do not include a study of the end-results as well.]

Pitzen [4] described a method of traction that had been used in Lange's Clinic in cases of dislocation of the hip. A dressing of zinc oxide glue was applied to the leg and covered with a plaster of paris cast. Then traction was applied up to 12 Kg. in an abducted position, which was gradually increased. As soon as the trochanter was pulled down to the height of the acetabulum the abduction was increased 120 degrees. With that method, Pitzen had been able to reduce severe dislocations with a high-standing head in patients up to the age of 8 years.

NUTRITIONAL DISTURBANCES OF THE BONE

Osteitis Fibrosa Cystica.—Hannon, Shorr, McClellan and Dubois,[5] Bauer, Albright and Aub,[6] and McClellan and Hannon [7] reported studies made in sequence in a case of osteitis fibrosa cystica. Studies were made particularly of the calcium and phosphorus metabolism. The calcium excretion remained constant at a fairly high level. A positive calcium balance with a high calcium intake was secured. The calcium metabolism was almost identical with that of a patient receiving daily 100 units of parathyroid extract-Collip. Two parathyroids were removed, the study of which revealed no abnormality. The calcium metabolism was unaffected by their removal. With a diet rich in

4. Pitzen: Ztschr. f. orth. Chir. **52**:529, 1929.

5. Hannon, R. R.; Shorr, E.; McClellan, W. S., and Dubois, E. F.: J. Clin. Investigation **8**:215, 1930.

6. Bauer, W.; Albright, F., and Aub, J. C.: J. Clin. Investigation **8**:229, 1930.

7. McClellan, W. S., and Hannon, R. R.: J. Clin. Investigation **8**:249, 1930.

calcium and with the addition of calcium lactate, roentgenograms showed a progressive increased density of bone and a decrease in the size of a cyst in the femur. Changes in phosphorus intake, which theoretically should affect the calcium, had no effect on calcium retention. Pituitary extract produced a marked increase in fecal calcium elimination, while thyroid extract increased the excretion of calcium in both urine and feces.

Spotted Bones.—Newcomet[8] described a single case of "spotted bones" or osteopoecilia which occurred in an Irishman aged 50. It was discovered accidentally when one hand was subjected to roentgen examination for a supposed fracture. The lesions were generalized in cancellous bone and were symptomless. The etiology was unknown and the prognosis good.

TUBERCULOSIS

Tuberculosis of the Hip.—Roederer[9] observed five patients with juxta-articular tuberculosis developing in the rim of the acetabulum and giving rise to disease of the hip. The process developed slowly, and it was a long time before symptoms appeared in the hip. This corresponded to the period of extra-articular osteitis. The diagnosis during this period was difficult. The roentgenogram often was not clear, particularly when the lesion was situated on the anterior or posterior lip of the acetabulum. Once the symptoms of arthritis had set in, the evolution was rapid.

Sorrel,[10] in a summary of his report to the thirty-eighth Congrès français de chirurgie (1929), discussed the indications and the results of fusion operations in Pott's disease. Two reasons made it difficult to appraise exactly the value of operations: The disease was greatly variable, as to both severity and type. In children, healing took place often with complete cicatrization of the lesion and bony fusion. In the adult, complete healing seldom took place. It was necessary to observe a large series of patients for a long time. A small series might give an entirely erroneous idea. The second reason was that it was not known exactly how to produce osteosynthesis. Was its action that of a splint to the spine alone or to the spine and the entire lesion? Did it modify the vascular supply? Was it simply palliative or really curative?

Sorrel advocated no operation in children. In adults, the operation was advisable, but it was difficult to decide on the time: in some instances the diagnosis could not definitely be made. In others, it was

8. Newcomet, W. S.: Am. J. Roentgenol. **22**:460, 1929.
9. Roederer, C.: Presse méd. **37**:1925, 1929.
10. Sorrel, E.: J. de chir. **34**:439, 1929.

difficult to determine if the lesion was inactive or healing under orthopedic measures. At all events, the operation should be performed at the period of least virulence. He used both the rigid graft of Albee and the flexible graft of Dijarier or Delangière. For cervical Pott's disease, he advocated a plaster bed; in others, a hard bed in the prone position for six months, and then a corset of plaster or celluloid for a year.

In 106 patients during ten years he had 60 excellent results, 21 good results, 9 neither good nor bad, and 16 bad. He noted that it was difficult to value the operation alone because of the associated general and orthopedic care.

INFANTILE PARALYSIS

Poliomyelitis Antistreptococcus Serum.—Rosenow [11] said that a streptococcus having peculiar neurotrophic and immunologic properties on isolation had again been cultivated from the throat, brain and cord, and for the first time in pure culture from the spinal fluid in cases of typical poliomyelitis occurring in another epidemic. It had been demonstrated consistently in smears of the spinal fluid in twenty-three patients and in each of twelve monkeys that had typical poliomyelitis following inoculation of virus. It was proved to be absent in the spinal fluid before the virus was injected.

The results from the use of poliomyelitis antistreptococcus serum were observed in the treatment of an additional series of patients with epidemic poliomyelitis and of monkeys with experimental poliomyelitis, in neutralization of virus in vitro, and in immunization of monkeys with the streptococcus against poliomyelitis virus.

The curative action of the serum in the treatment in this new series, as in several previous series of cases of poliomyelitis, seemed unmistakable and was manifested in one or more of several ways. Annoying symptoms, such as headache, pain, hyperesthesia, fever and a high pulse rate, often disappeared promptly. Paralysis seemed to be prevented if the serum was given in the preparalytic stage before there was marked evidence of involvement of the spinal cord. Progressive paralysis was seemingly arrested in many cases, including those with beginning bulbar symptoms, and the death rate and incidence of residual paralysis were markedly lowered.

The results obtained from serum treatment were in accord with those reported previously by Rosenow, Rowan, Sugg, Clarke and Dow, and Dively. The results from the use of the poliomyelitis antistrepto-

11. Rosenow, E. C.: Poliomyelitis Streptococcus Serum, J. A. M. A. **94**:777 (March 15) 1930.

coccus serum compared favorably with those reported by Aycock and Luther, from the use of convalescent serum. The total mortality rate (10 per cent) in this series of patients, as in those reported previously, was far lower, especially when the serum was given in the early stages of the disease (in which the mortality rate was 4 per cent), than in the control cases occurring in the same epidemic (33 per cent), and was far lower than that which usually occurred in this disease (25 per cent of 224 cases occurring in Minnesota in 1928).

Since the results from the use of this serum in the prevention and treatment of experimental poliomyelitis in monkeys were in agreement with the striking beneficial action again noted in clinical cases, it was concluded that poliomyelitis antistreptococcus serum, when properly prepared, had curative power in poliomyelitis. Its further trial, especially in the concentrated form in which serum reactions were largely eliminated, was indicated.

Epidemic of Poliomyelitis.—Lomer and Shirref [12] gave a résumé of the poliomyelitis epidemic in Ottawa in 1929. Of 181 patients suspected of having the disease, the diagnosis was established in 141, and these persons were treated; 109 patients recovered completely, 29 recovered with paralysis, 2 died with paralysis and 1 died without paralysis. Convalescent serum was given intramuscularly to all 115 patients admitted without paralysis; 109 of these patients recovered completely, 5 recovered with partial paralysis and 1 died without paralysis.

Experimental Poliomyelitis.—From a careful study of the epidemiology of poliomyelitis, Aycock [13] postulated a constant virus reservoir in a community through which the disease was disseminated by direct contact. In this way about one person in fifty was exposed each year, the exposure in most cases producing subclinical immunization. The disease occurred in children because they were the nonimmunized persons in the community. He expressed his belief that the cause of seasonal variation in a number of patients was not crowding of the schools, but a seasonal change in individual resistance. He felt that one can in no way control the virus, and that one's efforts should be directed toward raising individual resistance in the prevention and control of this disease.

Intradermal Immunization of Monkeys with One Set of Injections of Poliomyelitis Virus.—Rhoads [14] attempted to immunize four monkeys against poliomyelitis by one intradermal injection of poliomyelitis virus.

12. Lomer, T. A., and Shirref, W. T.: Canad. M. A. J. **22**:228, 1930.
13. Aycock, W. L.: Am. J. Pub. Health **20**:41, 1930.
14. Rhoads, C. P.: J. Exper. Med. **51**:1, 1930.

He gave multiple injections intradermally of 16 cc. of a 5 per cent saline suspension of the glycerolated spinal cord of a monkey infected with pooled, mixed poliomyelitis virus. In none of the monkeys were there any symptoms of poliomyelitis. One month later the monkeys were bled and neutralization tests were carried out. Active immunity was produced in each of the four monkeys.

[ED. NOTE.—Aycock's explanation is interesting and seems plausible. Rhoads' experiment in immunizing monkeys may be a stepping stone toward immunization of human beings. We doubt the willingness of anyone at present to be immunized with living virus]

PYOGENIC INFECTION

Osteochondritis of the Symphysis Pubis.—Pierson [15] reported four cases of nontuberculous osteochondritis of the symphysis pubis. Two cases followed suprapubic prostatectomy; infection presumably occurred at the time of operation or subsequently due to erosion from the closely apposed drainage tubes. One of these patients died of general sepsis. A third case occurred without apparent cause and was cleared up by drainage. The culture showed *Staphylococcus aureus*. The final case developed after a septic herniotomy. Pierson expressed his belief that this condition was probably more common than is usually supposed, as Beer had seen one case each year for the past twelve years. All the cases followed suprapubic prostatectomy, and recovery took place without drainage. The symptoms usually were tenderness over the symphysis pubis, pain down the legs and exaggeration of symptoms on motion. The roentgenograms helped relatively little as there is a wide variation in the roentgenograms of the normal pubic symphysis.

Juxta-Articular Osteitis.—From a study of 168 cases of juxta-articular osteitis of various types, Andrieu [16] concluded: 1. There are cases of osteitis in which the evolution, the diagnosis and the prognosis are profoundly modified by the fact that the condition is close to a joint. 2. These cases occur in persons of all ages, but are more common in infancy and particularly in early infancy. 3. The symptoms are not clearcut. The symptoms arising from the reaction in the adjacent joint are the most important. 4. In the presence of signs of chronic arthritis following successive abscesses, after having eliminated the various causes of articular inflammation, one need not make a diagnosis of rheumatism; one should always think of the possibility of a juxta-

15. Pierson, E. L.: Surg. Gynec. Obst. **49**:834, 1929.
16. Andrieu, M.: Rev. d'orthop. **16**:522, 1929.

articular osteitis. 5. The duration of the evolution can be extremely long. 6. The immediate prognosis depends on the menace of the osteitis to the neighboring joint. 7. The treatment must be directed toward preservation of the articulation. 8. In osteitis of the hips one must choose cases in which surgical approach seems easy; otherwise treatment should be conservative. 9. When either conservative or operative treatment is used, the joint must be immobilized until all symptoms have disappeared.

NEOPLASMS

Changes in Primary and Metastatic Tumors of the Bone Following Various Doses of Roentgen Rays.—Herendeen [17] said that the response of primary tumors of the bone or the changes induced by the application of a known amount of roentgen or radium rays could be predicted with a fair degree of accuracy provided that certain other information was available. First of all, one should know the age of the patient; equally important was detailed knowledge of the character of the tumor in a given case. By character was meant the degree of malignancy, rate of growth, size, location, origin and tendency to produce or destroy bone.

In the order of sensitivity to irradiation, primary tumors of the bone might be classified as follows: (1) endothelial myeloma or Ewing's tumor, (2) giant cell tumor, (3) multiple myeloma, (4) osteogenetic sarcoma of the destructive type, (5) osteogenetic sarcoma of the mixed or destructive and productive type and (6) osteogenetic sarcoma of the sclerosing, bone-producing type.

Herendeen warned against the use of heavy dosage in the treatment for giant cell tumors. Not only might heavy doses be followed by severe, unnecessary reactions or pathologic fractures, but more important, bone regeneration was likely to be retarded.

From the data accumulated to date, Herendeen concluded that roentgen treatment of giant cell tumors had passed the experimental stage and that with few exceptions the results from every angle were far superior to those secured by surgical measures.

Ewing's Sarcoma: Small Round Cell Sarcoma of the Bone.—Copeland, Geschickter and Bloodgood [18] studied sixty cases of Ewing's sarcoma. They found that it comprised 15 per cent of 400 cases of sarcoma of the bone. It was predominantly a disease of early life; 95 per cent of the patients were less than 25 years of age. There was a definite

17. Herendeen, R. E.: Radiology **13**:326, 1929.

18. Copeland, M. M.; Geschickter, C. F., and Bloodgood, J. C.: Ewing's Sarcoma; Small Round Cell Sarcoma of Bone, Arch. Surg. **20**:246 (Feb.) 1930.

history of trauma in 22 cases. Intermittent pain, increasing in severity and frequency, was the predominant symptom. A tumor, either small or involving the whole bone, was palpable in 90 per cent of the cases. The long bones were most frequently involved. Pathologic fractures were rare. Fever was observed with the metastases and often in the early stages with growth of the tumor. Bence-Jones bodies were never found in the urine. Except for occasional secondary anemia, nothing unusual was found in the blood. Roentgenograms showed a diffuse lesion near the midshaft. Increased density of bone with a widened cortex was the commonest observation. There was slight periosteal reaction with occasional osteophytes parallel to the cortex. Tumors in the soft parts were usually encapsulated by a thin fibrous tissue. The microscopic features were found to be the best criteria for diagnosis. The tumor consisted of small polyhedral cells in compact areas with round or oval nuclei and with scanty cytoplasm. Necrosis of cells was observed in areas a little removed from the blood vessels. In all cases in which metastases occurred (43 cases) the patients died. The commonest site for metastases was the lung; the skull, spine and scapula were next in frequency. The patients studied had lived from twenty months to nine years after the onset of symptoms, 8 of them being alive and apparently well. In most of the cases the first diagnosis had been inflammatory disease of the bone, a condition which the early roentgen appearance closely simulated. The treatment found to be best was: in the lower extremity, amputation below the upper third of the femur, followed by irradiation; in the upper extremity, resection followed by irradiation. From this study the authors could not determine the origin or histogenesis of the tumor.

Chondrosarcoma of the Bone.—Phemister [19] objected to the inclusion of chondrosarcoma under the heading of osteogenic sarcoma, as had been done in the present Registry of Bone Tumors. Of sixty-one cases of sarcoma of the bone studied he found ten which showed largely cartilaginous cells that could be designated as chondrosarcoma. Such tumors cast characteristic, blotchy, irregular shadows in the roentgenogram. Although they grew rapidly, they usually gave rise to metastases much later and consequently the prognosis was better. They might arise either centrally or peripherally in the ends of the bone shafts and might invade the veins, creating thrombus formation.

[Ed. Note.—Copeland et al. have summarized in admirable fashion their observations in this peculiar condition. Their work should be a

19. Phemister, D. B.: Surg. Gynec. Obst. **50**:216, 1930.

guide to any one who studies Ewing's tumors. The articles by Herendeen and Phemister are also enlightening, and make us feel that real progress is being made in the knowledge of tumors of the bone.]

ARTHRITIS

Calcium Metabolism in Arthritis.—Copp [20] made an intensive study of the calcium metabolism in one case of atrophic arthritis and in one case of hypertrophic arthritis. He found a retention of calcium in hypertrophic arthritis and a loss of calcium in atrophic arthritis. In general, he found that all acids increased the excretion of calcium. With sodium bicarbonate there was also an increased excretion of calcium. Phosphoric acid caused better retention of calcium than any other drugs administered. This acid was given in the dilute form, 20 drops before meals.

Results of Blood Culture in Acute Polyarthritis.—Jordan and Boland [21] studied the bacteriology of the blood in thirty-two cases of acute arthritis with multiple involvement of the joints. As controls they made blood cultures on sixteen patients in the same hospital who were suffering from various diseases, but with no involvement of the joints. In the cases of arthritis the diagnosis was acute rheumatic fever or subacute articular rheumatism. Of the sixty-seven blood cultures made in cases of arthritis, thirty-seven remained sterile for one month or longer, thirteen showed contaminations and sixteen showed organisms: a gram-negative short bacillus and a few plates on subculture, and a gram-positive club-shaped bacillus. No arthritis was produced in rabbits by the intravenous inoculation of these organisms. Of the twenty-three cultures made in control cases, sixteen remained sterile and seven showed contaminations.

[ED. NOTE.—The results of these authors seem as inconclusive as those of the many other workers who have attempted to study the bacteriologic aspects of arthritis. It seems impossible to isolate a specific organism at present, but it is hoped that some progress will eventually result from the vast amount of data being accumulated.]

Sympathetic Ganglionectomy.—Adson and Rowntree [22] have applied sympathectomy (lumbar and cervicodorsal) to cases of chronic polyarthritis. Patients were selected in whom the disease had not progressed

20. Copp, E. F. F.: Calcium Metabolism in Arthritis, Arch. Int. Med. **45**: 136 (Jan.) 1930.

21. Jordan, E. P., and Boland, J. P.: J. Infect. Dis. **46**:148, 1930.

22. Adson, A. W., and Rowntree, L. G.: Surg. Gynec. Obst. **50**:204, 1930.

far enough to cause destruction of the points and in whom all known foci of infection had been removed. The authors also drew attention to the vasospastic syndrome which had been temporarily relieved by baking, diathermy and vaccines. The presence of the vasospastic syndrome was determined in each case by Brown's "fever test" in which, after the injection of foreign protein, simultaneous readings of the temperatures of the mouth and skin were made. Sympathectomy had not been applied to arthritis of gonorrheal origin.

Six cases were carefully reported. In these sympathectomy had been done on either the lumber or the cervicodorsal sympathetic chain or both, depending on the extremities involved. Unless the arthritic destruction of the joint was too advanced to permit a return of function, the patients without exception improved. They gained weight, and the motion of the joint improved. The moisture, coldness and feeling of heaviness of the extremity diminished and the muscle power increased.

Parathyroidectomy in Ankylosing Polyarthritis.—Oppel [23] stated that his investigations and also those of three other Russian observers showed that a majority of the patients suffering with atrophic, ankylosing arthritis had a high calcium level in the blood and a decrease in the electro-excitation of the muscle. These conditions, he observed, were the opposite of those found in tetany. He therefore reasoned that parathyroidectomy might be indicated in such cases. Samarin found improvement in 33 per cent of forty-nine patients following the removal of two parathyroids. Oppel expressed his belief that such an operation primarily destroyed the hypercalcemia, stopped the progress of ankylosis and beneficially influenced the function of voluntary muscles.

[ED. NOTE.—This work seems highly experimental, and careful data are not presented to convince us that parathyroidectomy is justified in chronic arthritis.]

The Large Bowel in Chronic Arthritis.—Fletcher and Graham [24] made a roentgen examination of the large bowel in sixty patients with chronic arthritis. In 65 per cent of these patients they observed changes that they considered abnormal. There were changes in tone, haustral markings and length. Atony was sometimes seen in the whole colon, though usually in the cecum where it might be extreme. These abnormalities were markedly improved by dietetic treatment with coincident improvement in the arthritis.

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23. Oppel, W. A.: Ann. Surg. **90**:978, 1929.

24. Fletcher, A. A., and Graham, D.: Am. J. M. Sc. **179**:91, 1930.

The Colon in Relation to Chronic Arthritis.—Fishbaugh [25] emphasized the importance of eliminating the colon as a focus of infection in the patient with chronic arthritis. He had followed a series of sixty female and fourteen male patients, in whom, after all other foci had been eliminated, the colon was found to be the disturbing factor. The various etiologic factors were chronic constipation, chronic or subacute colitis, bands or adhesions, diverticula, rectal cyst or hemorrhoids. Roentgen examination of the colon for four or more successive days was of great aid in determining the diagnosis of sluggish colon. Except in cases requiring surgical measures, treatment consisted of a bulky diet, mild laxatives, and irrigations with a cecal tube. After irrigations an active culture of acidophilus was left in the cecum. Eight cases were not followed; of the remaining seventy-two, forty-two were quiescent, twenty-two showed improvement and eight no improvement after treatment.

Spondylitis Deformans.—Shanz [26] noted that the bony proliferations in spondylitis were more pronounced on the right side than on the left. He felt that on the left the aorta acted as a support to the spine. He thought that this same factor was involved in scoliosis in which the dorsal curve was toward the right in the majority of cases.

CIRCULATORY DISTURBANCES

Volkmann's Ischemic Paralysis.—Meyerding [27] reported on 128 cases of Volkmann's ischemic paralysis observed at the Mayo Clinic; in 36 of these operation was performed. The average age of the patients was 24 years and the average duration of the contracture, three years; the results were most encouraging in young patients with recent injury. The patients in group 1, with deformity of several days' or weeks' duration, whose hands showed the typical clawlike contracture, but whose arteries pulsated well and whose hands were warm, practically all responded to treatment with the Jones extension splint. Group 2 consisted of those who had deformity of several months' duration with cold hands and diminished pulsation, but whose fingers could still be brought out straight. These patients responded less favorably to the Jones method of treatment; yet one hesitated to operate until the treatment by gradual extension had been given a fair trial. Group 3 consisted of patients who were older and in whom the contracture was of

25. Fishbaugh, E. C.: Am. J. Surg. **7**:561, 1929.

26. Shanz, A.: Ztschr. f. orth. Chir. **53**:42, 1930.

27. Meyerding, H. W.: Volkmann's Ischemic Contracture, J. A. M. A. **94**: 394 (Feb. 8) 1930.

longer duration. These patients had marked deformity and atrophy, and because of contracture of the capsules the fingers and wrists could not be straightened easily, even with force. The pulsation was impaired and the muscles were ropelike on the flexor side. There were scars from sloughing with impairment of motion at the elbow and of supination. These patients demanded surgical procedures. Definite benefit could always be expected as far as correction of the deformity was concerned, but the loss of function in the muscles and the subsequent changes in the bones produced partial impairment of the extremity. There was little to be gained by the treatment of patients in group 4; although the deformity might be corrected by tenotomy and osteotomy, little function resulted and the impairment in circulation and the involvement of nerves sometimes necessitated amputation. A combination of gradual preoperative and postoperative extension with lengthening of the tendon and neurolysis followed by physiotherapy was often indicated.

Peripheral Vascular Diseases.—Adson and Brown [28] said that sympathetic ganglionectomy and trunk resection was a surgical procedure of considerable magnitude which one was justified in using in the treatment of patients with advanced Raynaud's disease, in the early developing vasospastic cases of scleroderma, in cases of thrombo-angiitis obliterans and in other cases in which vasospasm of the collateral arteries existed. The operation was probably indicated in other and borderline cases, but should be employed with caution, for the procedure was not a cure-all for all peripheral vascular diseases. The authors had operated on six patients with Raynaud's disease of the feet. In every case complete and permanent relief had been obtained. Four patients with scleroderma had been operated on. In early cases in which the scleroderma was less marked, the results had been excellent and a conservative estimate was from 70 to 80 per cent relief. They believed that more effective treatment of patients with scleroderma depended largely on early diagnosis and the institution of therapeutic surgical measures before fibrosis and atrophy had taken place. Operations had been performed on twenty patients with thrombo-angiitis obliterans of the lower extremity. Four of these had been failures in that amputation had had to be performed in from two weeks to a year after operation. In sixteen patients the surface temperature had increased, but not to the degree observed in Raynaud's disease. The increase in the elimination of

28. Adson, A. W., and Brown, G. E.: Thoracic and Lumbar Sympathetic Ganglionectomy in Peripheral Vascular Diseases, J. A. M. A. **94**:250 (Jan. 25) 1930.

heat, relief of pain and healing of ulcers had frequently been spectacular. In four cases thoracic sympathetic ganglionectomy had been performed for thrombo-angiitis obliterans affecting the hands. The results had been eminently satisfactory. The authors said that about one of every six or seven cases observed in the last two years had fulfilled requirements as far as the indications believed necessary for the operation were concerned.

DISEASES OF THE NERVOUS SYSTEM

Sympathectomy.—Leriche and Fontaine [29] studied (1) the cicatrization of sympathetic trunks which had been sectioned and (2) the pathologic rôle of neuromas of sympathetic cicatrization. On the basis of two observations, they believed that the cicatrization might explain the recurrence of symptoms after a period of amelioration. The symptoms might be topographically different, but of the same general type as the original trouble. Such cicatrices might greatly diminish the therapeutic value of sympathectomies.

Periodic Paralysis.—Yoshimura [30] observed that periodic paralysis of the extremities was often concurrent with diabetes or with glycosuria. Examination of blood drawn during an attack of paralysis showed that the magnesium content was far in excess of the calcium content. It is known that magnesium has a paralyzing effect on the neuromuscular apparatus. In experiments on animals the author observed that either the administration of the magnesium or the intravenous injection of dextrose led to typical paralysis of the extremities. In a patient to whom dextrose was administered during an attack of paralysis of the extremities the paralytic symptoms became more severe. After the injection of calcium, however, the paralysis subsided. On the basis of these observations the author concluded that the etiologic factor in periodic paralysis of the extremities was a shifting of the calcium-magnesium equilibrium of the blood serum.

Myeloradiculitis.—Strauss and Rabiner [31] reported seven cases of acute invasion of the nerve roots and spinal cord for which they had coined the name myeloradiculitis. In all cases there had been a rapid onset after slight malaise and with infection of the upper respiratory tract in most cases. The symptoms had been radiating pain, occasionally with areas of hypo-esthesia or hyperesthesia, and weakness of the

29. Leriche, R., and Fontaine, R.: J. de chir. **34**:439, 1929.

30. Yoshimura, K.: München. med. Wchnschr. **76**:1921, 1929.

31. Strauss, I., and Rabiner, A. M.: Myeloradiculitis, Arch. Neurol. & Psychiat. **23**:240 (Feb.) 1930.

extremities with flaccid paralysis in three cases. In several instances there had been transient disturbance of sphincter control. In all there had occurred rapid and practically complete recovery in from eighteen hours to two months. Intravenous typhoid therapy had been used, but recovery had been so rapid that its value in this condition could not be estimated.

[ED. NOTE.—The similarity between the cases reported and others that we have seen diagnosed poliomyelitis is striking. Further information will be required to give a clearer understanding of the difference, if any exists.]

(To be continued)